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(71) Applicant: SCICLONE PHARMACEUTICALS, INC. [US/US]; 901 Mariners Island Boulevard, San Mateo, CA 94404 (US).

(72) Inventors: RUDOLPH, Alfred, R.; 14142 Liddicoat Drive, Los Altos Hills, CA 94022 (US). TAM, Vincent, Chung-Yin; 35, Ventris Road, Happy Valley, Hong Kong (CN). QUAN, Maggie, Jie; Room 502, No. 16, Lane 336, E Mei Road, Shanghai 200080 (CN).

(74) Agents: REPPER, George, R. et al.; Rothwell, Figg, Ernst & Manbeck, P.C., Suite 701-E, 555 13th Street, N.W., Washington, DC 20004 (US).

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(54) Title: METHOD OF REDUCING SIDE EFFECTS OF CHEMOTHERAPY IN CANCER PATIENTS

(57) Abstract: A method for reducing the severity of chemotherapy side effects in cancer patients by administering thymosin α_1 in conjunction with the administration of a chemotherapy agent to the patient. As a result of the reduction of post-chemotherapy side effects, patients experience an increase in the quality of life.

METHOD OF REDUCING SIDE EFFECTS OF CHEMOTHERAPY IN CANCER PATIENTS

FIELD OF THE INVENTION

The present invention relates to improved treatment of cancer in animals, including humans, by reducing the side effects of chemotherapy.

BACKGROUND OF THE INVENTION

Cancers are a leading cause of death in animals and humans. The leading cancer therapies today are surgery, radiation and chemotherapy. In spite of advances in the field of cancer treatment, each of these known therapies has serious side effects. For example, surgery disfigures the patient or interferes with normal bodily functions. Chemotherapy or radiation therapies cause patients to experience acutc debilitating symptoms including nausea, vomiting, diarrhea, hypersensitivity to light, hair loss, etc. The side effects of these cytotoxic compounds frequently limit the frequency and dosage at which they can be administered.

Chemotherapeutic agents have been found useful in treating cancer in humans. Broadly classified as antineoplastics, chemotherapeutic agents found to be of assistance in the suppression of tumors include but are not limited to alkylating agents (e.g., nitrogen mustards), antimetabolites (e.g., pyrimidine analogs), radioactive isotopes (e.g., phosphorous and iodine), hormones (e.g., estrogens and adrenocorticosteroids), miscellaneous agents (e.g., substituted ureas) and natural products (e.g., vinca alkyloids and antibiotics). Although the preceding compounds are not curative agents, they are widely recognized in the medical profession as useful in the suppression, palliation, retardation and control of malignant tumors. While these compounds have been found to be effective and are in general clinical use as antiproliferative agents, there are well recognized drawbacks associated with their administration. The alkylating agents have marked cytotoxic action and the ability of these drugs to interfere with normal mitosis and cell division can be lethal. The antimetabolites can lead to anorexia, progressive weight loss, depression, and coma. Prolonged administration of antimetabolites can result in serious changes in bone marrow. Both the alkylating agents and the antimetabolites generally have a depressive effect on the immunosuppressive system. Prolonged administration of natural products such as vinca alkyloids can also result in bone marrow depression. Hydroxy urea and other chemically derived agents can lead to rapid reduction in levels of adrenocorticosteriods and their metabolites. The administration of hormonal compounds or radioactive isotopes is also

undesirable from the viewpoint of inflicting damage on the immunosuppressive system and thereby disabling the body's defenses against common infections. In most instances, it would be preferable to employ a chemotherapeutic agent which is effective in controlling, retarding, or suppressing the growth of malignant tumors while simultaneously acting to stimulate the patient's immune system.

SUMMARY OF THE INVENTION

In accordance with the present invention, a method is provided in which the side effects of chemotherapy in cancer patients are reduced by administering thymosin α_1 ("Tα_1") in conjunction with the administration of the chemotherapy agent to the patient. The reduction in the severity of post-chemotherapy side effects increases the quality of life experienced by patients receiving chemotherapy.

DETAILED DESCRIPTION OF THE INVENTION

It is known that the thymus produces a family of polypeptides termed thymosin and perhaps several other thymic hormones and/or factors which play an important role in the maturation, differentiation and function of T-cells. Thymosin has been found to induce T-cell differentiation and enhance immunological functions in genetically athymic mice, in adult thymectisized mice and in NZB mice with severe autoimmune reactions, in tumor bearing mice and in mice with casein-induced amyloidosis.

Thymosin α_1, an acidic polypeptide isolated from thymosin fraction 5 is an immunomodulator that acts primarily by enhancing T-cell function and also has been shown to have direct anti-cancer effects. Thymosin α_1 has been found to stimulate T-cell maturation, differentiation and function.

It has been previously documented that thymosin α_1 reduces the incidence and severity of post-chemotherapy infections. It has now been found that the use of thymosin α_1 in conjunction with the administration of antineoplastics (chemotherapeutic agents) significantly improves the cancer patient's quality of life by reducing nausea, vomiting, loss of appetite, inability to sleep, decline in overall feeling, reduction in daily activity, fatigue and depression. The administration of thymosin α_1 does not appear to result in any side effects.

The mechanism by which thymosin α_1 acts to improve the patient quality of life is not yet known. Without being bound to any particular theory, one possibility may relate to the apparent ability of thymosin α_1 to block neurotransmitter receptors. It is believed that most

chemotherapeutic agents activate the chemoreceptor trigger zone (CTZ) and that the CTZ chemotherapy interaction triggers the release of neurotransmitters that activate the vomiting center. CTZ neurotransmitters that are thought to cause emesis include but are not limited to, dopamine, serotonin, histamine, norepinephrine, apomorphine, neurotensin, vasoactive intestinal polypeptide (VIP). In vitro and in vivo studies, have shown that thymosin α_1 has a VIP receptor blocking effect. This may explain why thymosin α_1 can control vomiting in patients whose vomiting could not be controlled by 5-HT blockers.

The increase in quality of life may be due to thymosin α_1's ability to control GI adverse effects like nausea and vomiting through the above described VIP receptor blocking effect or it could be the result of a reduction of low grade, clinically undetectable infections or some combination thereof.

In one embodiment of the present invention, the thymosin α_1 is administered prior to the administration of the chemotherapy. The thymosin α_1 may be administered on a single day or be administered on several days prior to the chemotherapy.

In another embodiment of the invention, the thymosin α_1 is administered following the administration of the antineoplastic agent. In this embodiment, the thymosin α_1 may be administered once or several times prior to the chemotherapy. This administration may take place on a single day or on a series of days prior to the administration of the antineoplastic agent.

In another embodiment of the invention, thymosin α_1 is administered prior to and subsequent to the administration of the antineoplastic agent. This administration may take place on one or multiple days prior to and one or multiple days subsequent to the chemotherapy.

In one preferred embodiment, thymosin α_1 is administered to cancer patients once each day on four days immediately preceding the administration of the antineoplastic agent and once on day 2 and on day 4 following chemotherapy.

$T\alpha_1$ can be administered in any suitable way, such as by injection, infusion, or transcutaneously. Other methods of administration may also be possible, such as orally as a liquid or solid dosage form. In preferred embodiments $T\alpha_1$ is injected.

Thymosin α_1 may be administered at any suitable dosage level, e.g., within a range of about 0.1 - 3 mg. In preferred embodiments, thymosin α_1 is administered via injection at a dosage of about 1.6 mg s.c.

Thymosin α_1 can be administered to reduce side effects of any suitable antineoplastic agents, including one or more antineoplastic agent selected from the group consisting of alkylating agents (e.g., nitrogen mustards), antimetabolites (e.g., pyrimidine analogs), radioactive

isotopes (e.g., phosphorous and iodine), hormones (e.g., estrogens and adrenocorticosteroids), miscellaneous agents (e.g., substituted ureas) and natural products (e.g., vinca alkyloids and antibiotics). Examples of such anitneoplastic agents include but are not limited to the following:

ADJUNCT ANTINEOPLASIC THERAPY:

Aloprim™ for Injection

Anzemet® Injection

Anzemet® Tablets

Aredia® for Injection

Didronel® I.V. Infusion

Diflucan® Tablets, Injection, and Oral Suspension

Epogen® for Injection

Ergamisol® Tablets

Ethyol® for Injection

Kytril® Injection

Kytril® Tablets

Leucovorin Calcium for Injection

Leucovorin Calcium Tablets

Leukine®

Marinol® Capsules

Mesnex® Injection

Neupogen® for Injection

Procrit® for Injection

Salagen® Tablets

Sandostatin® Injection

Zinecard® for Injection

Zofran® Injection

Zofran® ODT™ Orally Disintegrating Tablets

Zofran® Oral Solution

Zofran® Tablets

Zyloprim® Tablets

ALKYLATING AGENTS:

Myleran® Tablets

Paraplatin® for Injection

Platinol® for Injection

Platinol-AQ® Injection

Thioplex® for Injection

NITROGEN MUSTARDS:

Alkeran® for Injection

Alkeran® Tablets

Cytoxan® for Injection

Cytoxan® Tablets

Ifex® for Injection

Leukeran® Tablets

Mustargen® for Injection

NITROSOUREAS:

BiCNU®

CeeNU®

Gliadel® Wafer

Zanosar® Sterile Powder

ANTIBIOTICS:

Adriamycin® PFS/RDS for Injection

Blenoxane®

Cerubidine® for Injection

Cosmegen® for Injection

DaunoXome®

Doxil® Injection

Doxorubicin Hydrochloride for Injection, USP

Idamycin PFS Injection

Mithracin® for Intravenous Use

Mutamycin® for Injection

Nipent® for Injection

Novantrone® for Injection

Rubex® for Injection

Valstar™ Sterile Solution for Intravesical Instill

Lupron® Injection

Zoladex®

PROGESTINS

Depo-Provera® Sterile Aqueous Suspension

Megace® Tablets

IMMUNOMODULATORS

Ergamisol® Tablets

Proleukin® for Injection

MISCELLANEOUS ANTINEOPLASTICS

Camptosar® Injection

Celestone® Soluspan® Suspension

DTIC-Dome®

Elspar® for Injection

Etopophos® for Injection

Etoposide Injection

Gemzar® for Injection

Herceptin® I.V.

Hexalen® Capsules

Hycamtin® for Injection

Hydrea® Capsules

Hydroxyurea Capsules, USP

Intron® A for Injection

Lysodren® Tablets

Matulane® Capsules

Navelbine® Injection

Oncapsar®

Oncovin® Solution Vials and Hyporets

Ontak™ Vials

Proleukin® for Injection

Rituxan™ for Infusion

Rituxan® I.V.

Roferon®-A Injection

Taxol® Injection

Taxotere® for Injection Concentrate

TheraCys®

Tice® BCG Vaccine, USP

Velban® Vials

VePesid® Capsules

VePesid® for Injection

Vesanoid® Capsules

Vumon® for Injection

PHOTOSENSITIZING AGENTS

Photofrin® for Injection

SKIN AND MUCUS MEMBRANE AGENTS

Efudex® Cream

Efudex® Topical Solution

Fluoroplex® Topical Cream

Fluoroplex® Topical Solution

The invention is illustrated by the following Example, which is not intended to be limiting.

Example 1

METHOD: A randomized crossover open label trial was performed. A total of sixty patients, twenty with lung cancer, twenty with gastric cancer and twenty with breast cancer were studied during two complete cycles of chemotherapy. All patients were randomized into two groups. In group 1, patients received chemotherapy with thymosin α_1 in the first cycle, and without thymosin α_1 in the second cycle. While patients in group 2 received chemotherapy without thymosin α_1 in the first cycle, and with thymosin α_1 in the second cycle. The patients were treated as follows:

Twenty lung cancer patients were treated with 100 mg of Etoposide IV on days 1-5 and 40 mg of Cisplatin I.V. on days 1-3 in a 21 day cycle.

Twenty gastric cancer patients were treated with 100 mg of Etoposide IV on days 1-5, 30 mg/m^2 Calcium Leucovorin I.V. on days 1-5 and 500 mg/m^2 5-Fluorouricil (5-FU) I.V. on days 1-5.

Twenty breast cancer patients were treated with 5-Fluorouricil 500 mg/m^2, Adriamycin I.V. 30 mg/m^2 I.V. on day 1 and cyclophosphamide 500 mg/m^2 I.V. on day 1.

A mild anti-emetic consisting of 20 mg metoclopamide, I.M. and 5 mg Dexamethasone I.V. were given to all patients on days 1-5. All subjects on thymosin received six injections of 1.6 mg s.c. $T\alpha_1$ on each of the four days immediately preceding the chemotherapy and on days two and four following chemotherapy. All patients who have completed the two cycles of chemotherapy, then were reallocated into two cohorts, A and B. Cohort A are patients with $T\alpha_1$, and Cohort B are patients without $T\alpha_1$.

ANALYSIS: Quality of life was analyzed using a scored scale for (1) loss of appetite, (2) loss of sleep, (3) fatigue, (4) reduction in daily activity, (5) decline in overall feeling, (6) depression and (7) nausea and vomiting. Maximum total score was 35 points.

RESULTS: A comparison between cycles (with $T\alpha_1$ and without $T\alpha_1$) was performed. The addition of $T\alpha_1$ to chemotherapy cycles significantly increases the quality of life scores compared with cycles without $T\alpha_1$.

Side Effects

Loss of Appetite	4.33 vs. 3.99	p = 0.0001
Loss of Sleep	4.41 vs. 4.10	p = 0.002
Fatigue	4.05 vs. 3.70	p = 0.0001
Reduction in Daily Activity	4.12 vs. 3.84	p = 0.0001
Decline in Overall Feeling	4.32 vs. 3.94	p = 0.0001
Depression	4.01 vs. 3.72	p = 0.003
Nausea and Vomiting	4.29 vs. 3.93	p = 0.001

Nausea and vomiting classified according to WHO criteria:

Group	n	Grade 0	Gr.1	Gr.2	Gr.3	Gr.4	P value
A (with $T\alpha_1$)	54	7/55	33	13	1	0	P<0.0005
B (Without $T\alpha_1$)	53	4/53	19	19	11	0	

CONCLUSION: Adding $T\alpha_1$ to chemotherapy significantly improves patient quality of life.

CLAIMS

1. A method of reducing side effects of chemotherapy in a cancer patient, comprising administering to a cancer patient thymosin α_1 ($T\alpha_1$) in conjunction with administration of a chemotherapy agent to said patient.

2. The method of claim 1 wherein the $T\alpha_1$ is administered prior to administration of said chemotherapy agent.

3. The method of claim 1 wherein said $T\alpha_1$ is administered subsequent to said chemotherapy agent.

4. The method of claim 1 wherein said $T\alpha_1$ is administered both prior to and subsequent to said chemotherapy agent.

5. The method of claim 2 wherein said $T\alpha_1$ is administered during a plurality of administrations on a plurality of days prior to said chemotherapy agent.

6. The method of claim 2 wherein said $T\alpha_1$ is administered as a single administration on each of a plurality of days prior to said chemotherapy agent.

7. The method of claim 2 wherein a single administration of $T\alpha_1$ is administered one day immediately prior to administration of said chemotherapy agent.

8. The method of claim 2 wherein a single administration of $T\alpha_1$ is administered on each of two days immediately prior to administration of said chemotherapy agent.

9. The method of claim 2 wherein a single administration of $T\alpha_1$ is administered on each of three days immediately prior to administration of said chemotherapy agent.

10. The method of claim 2 wherein a single administration of $T\alpha_1$ is administered on each of four days immediately prior to administration of said chemotherapy agent.

11. The method of claim 3 wherein a plurality of administrations of said $T\alpha_1$ are administered on a plurality of days subsequent to administration of said chemotherapy agent.

12. The method of claim 3 wherein a single administration of $T\alpha_1$ is administered on each of a plurality of days subsequent to administration of said chemotherapy agent.

13. The method of claim 3 wherein a single administration of $T\alpha_1$ is administered one day immediately subsequent to administration of said chemotherapy agent.

14. The method of claim 3 wherein a single administration of $T\alpha_1$ is administered on each of two days immediately subsequent to said administration of said chemotherapy agent.

15. The method of claim 4 wherein a plurality of administrations of said $T\alpha_1$ are administered on a plurality of days prior to and subsequent to the administration of said chemotherapy agent.

16. The method of claim 4 wherein a single administration of $T\alpha_1$ is administered on each of a plurality of days prior to and subsequent to the administration of said chemotherapy agent.

17. The method of claim 4 wherein a single administration of $T\alpha_1$ is administered one day immediately prior to and one day immediately subsequent to administration of said chemotherapy agent.

18. The method of claim 4 wherein a single administration of $T\alpha_1$ is administered on each of two days immediately days prior to and two days immediately subsequent to the administration of said chemotherapy agent.

19. The method of claim 1 wherein $T\alpha_1$ is administered at a dosage within a range of about .1 - 3.2 mg.

20. The method of claim 1 wherein $T\alpha_1$ is administered at a dosage of about 1.6 mg.

21. The method of claim 1 wherein said chemotherapy agent is selected from the group consisting of antineoplastic alkylating agents, antineoplastic antimetabolites, antineoplastic radioactive isotopes, antineoplastic hormones, antineoplastic ureas, antineoplastic vinca alkaloids, antineoplastic antibiotics, and combinations thereof.

22. The method of claim 21 wherein said antineoplastic alkylating agents are nitrogen mustards, said antineoplastic antimetabolites are pyrimidine analogs, said antineoplastic radioactive isotopes are radioactive phosphorous, radioactive iodine or a combination thereof, and said antineoplastic hormones are estrogens, adrenocorticosteroids, and combinations thereof.

23. The method of claim 1 wherein said chemotherapy agent is selected from the group consisting of: allopurinol sodium, dolasetron mesylate, pamidronate disodium, etidronate, fluconazole, epoetin alfa, levamisole HCL, amifostine, granisetron HCL, leucovorin calcium, sargramostim, dronabinol, mesna, filgrastim, pilocarpine HCl, octreotide acetate, dexrazoxane, ondansetron HCl, ondansetron, busulfan, carboplatin, cisplatin, thiotepa, melphalan HCl, melphalan, cyclophosphamide, ifosfamide, chlorambucil, mechlorethamine HCl, carmustine, lomustine, polifeprosan 20 with carmustine implant, streptozocin, doxorubicin HCl, bleomycin sulfate, daunirubicin HCl, dactinomycin, daunorucbicin citrate, idarubicin HCl, plimycin, mitomycin, pentostatin, mitoxantrone, valrubicin, cytarabine, fludarabine phosphate, floxuridine, cladribine, methotrexate, mercaptipurine, thioguanine, capecitabine, methyltestosterone, nilutamide, testolactone, bicalutamide, flutamide, anastrozole, toremifene citrate, tamoxifen, estramustine phosphate sodium, ethinyl estradiol, estradiol, esterified estrogens, conjugated estrogens, leuprolide acetate, goserelin acetate, medroxyprogesterone acetate, megestrol acetate, levamisole HCl, aldesleukin, irinotecan HCl, dacarbazine, asparaginase, etoposide phosphate, gemcitabine HCl, trastuzumab, altretamine, topotecan HCl, hydroxyurea, interferon alfa-2b, recombinant, mitotane, procarbazine HCl, vinorelbine tartrate, *E. coli* L-asparaginase, *Erwinia* L-asparaginase, vincristine sulfate, denileukin diftitox, aldesleukin, rituximab, interferon alfa-2a, recombinant, paclitaxel, docetaxel, BCG live (intravesical), vinblastine sulfate, etoposide, tretinoin, teniposide, porfimer sodium, fluorouracil, betamethasone sodium phosphate and betamethasone acetate, letrozole, and combinations thereof.

24. The method of claim 1 wherein said chemotherapy agent is selected from the group consisting of etoposide citrororum factor, folinic acid, calcium leucouorin, 5-fluorouricil, adriamycin, cytoxan, diamino dichloro platinum and combinations thereof.

25. The method of claim 1 wherein said side effects are selected from the group consisting of loss of appetite, loss of sleep, fatigue, reduction in daily activity, decline in overall feeling, depression, nausea and vomiting and combinations thereof.

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(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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According to international Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	E. GARACI ET AL.: "SEQUENTIAL CHEMOIMMUNOTHERAPY FOR ADVANCED NON-SMALL CELL LUNG CANCER USING CISPLATIN, ETOPOSIDE, THYMOSIN-ALPHA1 AND INTERFERON-ALPHA2A" EUROPEAN JOURNAL OF CANCER, PERGAMON PRESS, OXFORD, GB, vol. 31A, no. 13/14, 1995, pages 2403-2405, XP001042211 ISSN: 0959-8049 page 2404, right-hand column, line 4 - line 12; table 2 page 2404, last paragraph --- -/--	1-25

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevence

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Date of the actual completion of the international search	Date of mailing of the international search report
16 January 2002	30/01/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ryckebosch, A

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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(71) Applicant *(for all designated States except US)*: **TULARIK INC.** [US/US]; Two Corporate Drive, South San Francisco, CA 94080 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SCHWENDNER, Susan** [US/US]; 2000 Crystal Springs Road, #7-05, San Bruno, CA 94066 (US). **TIMMERMANS, Pieter** [NL/US]; 850 Hillcrest Drive, Redwood City, CA 94062 (US). **WALLING, Jacqueline** [GB/US]; 2710 Easton Drive, Burlingame, CA 94010 (US).

(74) Agents: **KEZER, William, B.** et al.; Townsend and Townsend and Crew LLP, Two Embarcadero Center, Eighth Floor, San Francisco, CA 94111 (US).

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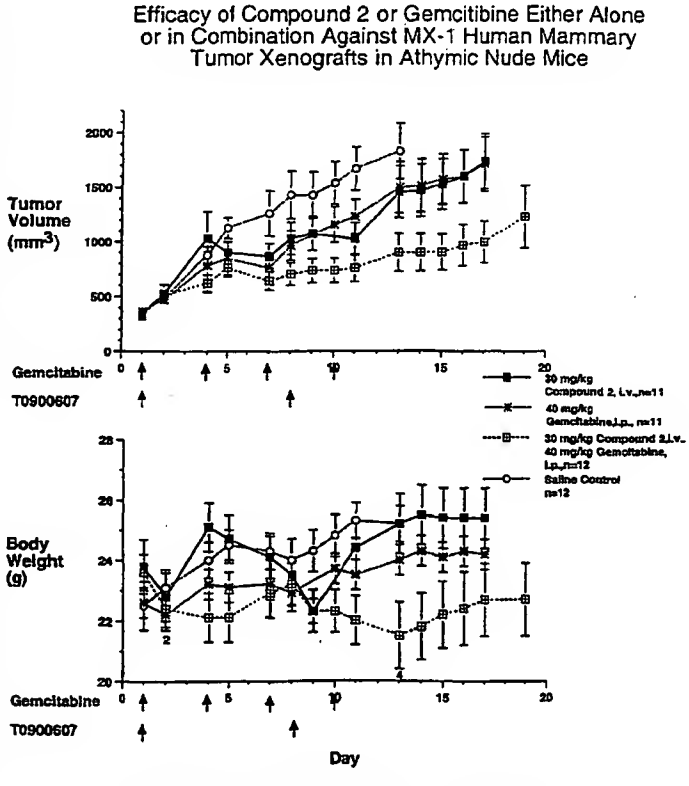
(54) Title: COMBINATION THERAPY USING PENTAFLUOROBENZENESULFONAMIDES AND ANTINEOPLASTIC AGENTS



Arrow indicates dose administration. Results are expressed as the mean ± SEM.

(57) Abstract: Combination therapies are provided for the treatment of proliferative disorders which use a pentafluorobenzenesulfonamide of formula I and an antineoplastic agent such as gemcitabine or paclitaxel.

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COMBINATION THERAPY USING PENTAFLUOROBENZENESULFONAMIDES AND ANTINEOPLASTIC AGENTS

CROSS-REFERENCES TO RELATED APPLICATIONS

This application claims the benefit of USSN 60/245,878, filed November 3, 2000, the disclosure of which is incorporated herein by reference. Also, this application is related in technology to co-pending application Serial Number 09/627,041, filed July 27, 2000.

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

Not applicable

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates to combinations of pentafluorobenzenesulfonamides and various other chemotherapeutic agents that are capable of inhibiting abnormal cell proliferation.

BACKGROUND

Cancer is a generic name for a wide range of cellular malignancies characterized by unregulated growth, lack of differentiation, and the ability to invade local tissues and metastasize. These neoplastic malignancies affect, with various degrees of prevalence, every tissue and organ in the body. A multitude of therapeutic agents have been developed over the past few decades for the treatment of various types of cancer. The most commonly used types of anticancer agents include: DNA-alkylating agents (*e.g.*, cyclophosphamide, ifosfamide), antimetabolites (*e.g.*, methotrexate, a folate antagonist, and 5-fluorouracil, a pyrimidine antagonist), microtubule disrupters (*e.g.*, vincristine, vinblastine, paclitaxel), DNA intercalators (*e.g.*, doxorubicin, daunomycin),

and hormone therapy (*e.g.*, tamoxifen, flutamide). The ideal antineoplastic drug would kill cancer cells selectively, with a wide therapeutic index relative to its toxicity towards non-malignant cells. It would also retain its efficacy against malignant cells, even after prolonged exposure to the drug. Unfortunately, none of the current chemotherapies possess an ideal profile. Most possess very narrow therapeutic indexes and, in practically every instance, cancerous cells exposed to slightly sublethal concentrations of a chemotherapeutic agent will develop resistance to such an agent, and quite often cross-resistance to several other antineoplastic agents.

The development of new anticancer agents has given rise to new treatment regimens and new combinations that are proving more effective in combating this disease.

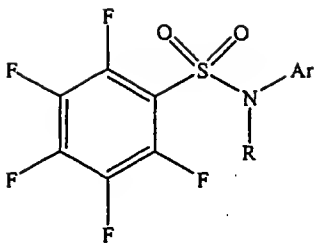
Accordingly, it is one object of the present invention to provide compositions which directly or indirectly are toxic to actively dividing cells and are useful in the treatment of cancer.

A further object of the present invention is to provide methods for killing actively proliferating cells, such as cancerous, bacterial, or epithelial cells, and treating all types of cancers, and generally proliferative conditions. A further object is to provide methods for treating other medical conditions characterized by the presence of rapidly proliferating cells, such as psoriasis and other skin disorders.

Additional objects, features and advantages will become apparent to those skilled in the art from the following description and claims.

SUMMARY OF THE INVENTION

In one aspect, the present invention provides compositions useful for the treatment of cancer and other diseases associated with abnormal cell proliferation. The compositions comprise an antineoplastic agent, including but not limited to prodrugs thereof, pharmaceutically acceptable salts of these agents and a compound having the formula:



(I).

In the formula above, the letter R represents a hydrogen, substituted or unsubstituted (C_1-C_{10})alkyl, or substituted or unsubstituted (C_3-C_6)alkenyl. The symbol Ar represents a substituted or unsubstituted aryl group or a substituted or unsubstituted heteroaryl group.

Suitable antineoplastic or antiproliferative agents include, but are not limited to, DNA-alkylating agents (e.g., cyclophosphamide, BCNU, busulfan and temozolamide), antimetabolites, antifolates and other inhibitors of DNA synthesis (e.g., methotrexate, 5-fluorouracil, gemcitabine), microtubule disruptors (e.g., vincristine, vinorelbine, paclitaxel, docetaxel), DNA intercalators (e.g., doxorubicin, daunomycin), hormone agents (e.g., tamoxifen, flutamide), topoisomerase I/II inhibitors and DNA repair agents (e.g., hydroxyurea, camptothecin, etoposide), growth factor receptor kinase inhibitors (e.g., AG1478 and AG1296), biological response modifiers (including cytokines such as interferon α and growth factor inhibitors), antiangiogenic and antivascular agents (e.g., combretastatin A-4), and other agents such as immunoconjugates (e.g., trasuzamab) and antisense oligonucleotides.

The compositions will, in some embodiments, contain a pharmaceutically acceptable carrier or diluent.

In another aspect, the present invention provides methods for the treatment of cancer and other proliferative disorders using the compositions provided above, or using the components in a sequential or simultaneous administration.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph which illustrates the effects of Compound 2 with gemcitabine in the treatment of MX-1 human mammary tumor xenografts in athymic nude mice, using suboptimal doses of each of the agents.

Figure 2 is a graph which illustrates the effects of Compound 2 with paclitaxel in the treatment of MX-1 human mammary tumor xenografts in athymic nude mice, using suboptimal doses of each of the agents.

Figure 3 provides the structures of Compound 1, Compound 2 and Compound 3.

DESCRIPTION OF THE SPECIFIC EMBODIMENTS

Definitions

The term "alkyl," by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain, or cyclic hydrocarbon radical, or combination thereof, which may be fully saturated, mono- or polyunsaturated and can include di- and multivalent radicals, having the number of carbon atoms designated (*i.e.* C_1-C_{10} means one to ten carbons). Examples of saturated hydrocarbon radicals include groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, cyclohexyl, (cyclohexyl)methyl, cyclopropylmethyl, homologs and isomers of, for example, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like. An unsaturated alkyl group is one having one or more double bonds or triple bonds. Examples of unsaturated alkyl groups include vinyl, 2-propenyl, crotyl, 2-isopentenyl, 2-(butadienyl), 2,4-pentadienyl, 3-(1,4-pentadienyl), ethynyl, 1- and 3-propynyl, 3-butynyl, and the higher homologs and isomers. The term "alkyl," unless otherwise noted, is also meant to include those derivatives of alkyl defined in more detail below as "heteroalkyl." Alkyl groups which are limited to hydrocarbon groups are termed "homoalkyl".

The term "alkylene" by itself or as part of another substituent means a divalent radical derived from an alkane, as exemplified by $-CH_2CH_2CH_2CH_2-$, and further includes those groups described below as "heteroalkylene." Typically, an alkyl (or alkylene) group will have from 1 to 24 carbon atoms, with those groups having 10 or fewer carbon atoms being preferred in the present invention. A "lower alkyl" or "lower alkylene" is a shorter chain alkyl or alkylene group, generally having eight or fewer carbon atoms.

The terms "alkoxy," "alkylamino" and "alkylthio" (or thioalkoxy) are used in their conventional sense, and refer to those alkyl groups attached to the remainder of the molecule via an oxygen atom, an amino group, or a sulfur atom, respectively.

The term "heteroalkyl," by itself or in combination with another term, means, unless otherwise stated, a stable straight or branched chain, or cyclic hydrocarbon radical, or combinations thereof, consisting of the stated number of carbon atoms and from one to three heteroatoms selected from the group consisting of O, N, Si and S, and wherein the nitrogen and sulfur atoms may optionally be oxidized and the nitrogen heteroatom may optionally be quaternized. The heteroatom(s) O, N and S may be placed at any interior position of the heteroalkyl group. The heteroatom Si may be placed at any position of the heteroalkyl group, including the position at which the alkyl group is attached to the remainder of the molecule. Examples include $-CH_2-CH_2-O-CH_3$, $-CH_2-CH_2-NH-CH_3$, $-CH_2-CH_2-N(CH_3)-CH_3$, $-CH_2-S-CH_2-CH_3$, $-CH_2-CH_2,-S(O)-CH_3$, $-CH_2-CH_2-S(O)_2-CH_3$, $-CH=CH-O-CH_3$, $-Si(CH_3)_3$, $-CH_2-CH=N-OCH_3$, and $-CH=CH-N(CH_3)-CH_3$. Up to two heteroatoms may be consecutive, such as, for example, $-CH_2-NH-OCH_3$ and $-CH_2-O-Si(CH_3)_3$. Similarly, the term "heteroalkylene" by itself or as part of another substituent means a divalent radical derived from heteroalkyl, as exemplified by $-CH_2-CH_2-S-CH_2CH_2-$ and $-CH_2-S-CH_2-CH_2-NH-CH_2-$. For heteroalkylene groups, heteroatoms can also occupy either or both of the chain termini (*e.g.*, alkyleneoxy, alkylenedioxy, alkyleneamino, alkylenediamino, and the like). Still further, for alkylene and heteroalkylene linking groups, no orientation of the linking group is implied.

The terms "cycloalkyl" and "heterocycloalkyl", by themselves or in combination with other terms, represent, unless otherwise stated, cyclic versions of "alkyl" and "heteroalkyl", respectively. Additionally, for heterocycloalkyl, a heteroatom can occupy the position at which the heterocycle is attached to the remainder of the molecule. Examples of cycloalkyl include cyclopentyl, cyclohexyl, 1-cyclohexenyl, 3-cyclohexenyl, cycloheptyl, and the like. Examples of heterocycloalkyl include 1 -(1,2,5,6-tetrahydropyridyl), 1-piperidinyl, 2-piperidinyl, 3-piperidinyl, 4-morpholinyl, 3-morpholinyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, 1 -piperazinyl, 2-piperazinyl, and the like.

The terms "halo" or "halogen," by themselves or as part of another substituent, mean, unless otherwise stated, a fluorine, chlorine, bromine, or iodine atom. Additionally, terms such as "haloalkyl," are meant to include monohaloalkyl and polyhaloalkyl. For example, the term "halo(C_1-C_4)alkyl" is meant to include trifluoromethyl, 2,2,2-trifluoroethyl, 4-chlorobutyl, 3-bromopropyl, and the like.

The term "aryl" means, unless otherwise stated, a polyunsaturated, typically aromatic, hydrocarbon substituent which can be a single ring or multiple rings

(up to three rings) which are fused together or linked covalently. The term "heteroaryl" refers to aryl groups (or rings) that contain from zero to four heteroatoms selected from N, O, and S, wherein the nitrogen and sulfur atoms are optionally oxidized, and the nitrogen atom(s) are optionally quaternized. A heteroaryl group can be attached to the remainder of the molecule through a heteroatom. Non-limiting examples of aryl and heteroaryl groups include phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 3-pyrazolyl, 2-imidazolyl, 4-imidazolyl, pyrazinyl, 2-oxazolyl, 4-oxazolyl, 2-phenyl-4-oxazolyl, 5-oxazolyl, 3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidyl, 4-pyrimidyl, 5-benzothiazolyl, purinyl, 2-benzimidazolyl, 5-indolyl, 1-isoquinolyl, 5-isoquinolyl, 2-quinoxalinyl, 5-quinoxalinyl, 3-quinolyl, and 6-quinolyl. Substituents for each of the above noted aryl and heteroaryl ring systems are selected from the group of acceptable substituents described below.

For brevity, the term "aryl" when used in combination with other terms (*e.g.*, aryloxy, arylthioxy, arylalkyl) includes both aryl and heteroaryl rings as defined above. Thus, the term "arylalkyl" is meant to include those radicals in which an aryl group is attached to an alkyl group (*e.g.*, benzyl, phenethyl, pyridylmethyl and the like) including those alkyl groups in which a carbon atom (*e.g.*, a methylene group) has been replaced by, for example, an oxygen atom (*e.g.*, phenoxymethyl, 2-pyridyloxymethyl, 3-(1-naphthyloxy)propyl, and the like).

Each of the above terms (*e.g.*, "alkyl," "heteroalkyl," "aryl" and "heteroaryl") are meant to include both substituted and unsubstituted forms of the indicated radical. Preferred substituents for each type of radical are provided below.

Substituents for the alkyl and heteroalkyl radicals (including those groups often referred to as alkylene, alkenyl, heteroalkylene, heteroalkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, and heterocycloalkenyl) can be a variety of groups selected from: -OR', =O, =NR', =N-OR', -NR'R", -SR', -halogen, -SiR'R"R"', -OC(O)R', -C(O)R', -CO_2R', -CONR'R", -OC(O)NR'R", -NR"C(O)R', -NR'-C(O)NR"R"', -NR"$C(O)_2$R', -NH-$C(NH_2)$=NH, -NR'$C(NH_2)$=NH, -NH-$C(NH_2)$=NR', -S(O)R', -$S(O)_2$R', -$S(O)_2$NR'R", -CN and -NO_2 in a number ranging from zero to (2m'+1), where m' is the total number of carbon atoms in such radical. R', R" and R"' each independently refer to hydrogen, unsubstituted (C_1-C_8)alkyl and heteroalkyl, unsubstituted aryl, aryl substituted with 1-3 halogens, unsubstituted alkyl, alkoxy or thioalkoxy groups, or aryl-(C_1-C_4)alkyl groups. When R' and R" are attached to the same

nitrogen atom, they can be combined with the nitrogen atom to form a 5-, 6-, or 7-membered ring. For example, -NR'R" is meant to include 1-pyrrolidinyl and 4-morpholinyl. From the above discussion of substituents, one of skill in the art will understand that the term "alkyl" is meant to include groups such as haloalkyl (*e.g.*, $-CF_3$ and $-CH_2CF_3$) and acyl (*e.g.*, $-C(O)CH_3$, $-C(O)CF_3$, $-C(O)CH_2OCH_3$, and the like).

Similarly, substituents for the aryl and heteroaryl groups are varied and are selected from: -halogen, -OR', -OC(O)R', -NR'R", -SR', -R', -CN, $-NO_2$, $-CO_2R'$, -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(O)R', $-NR"C(O)_2R'$, ,-NR'-C(O)NR"R"', $-NH-C(NH_2)=NH$, $-NR'C(NH_2)=NH$, $-NH-C(NH_2)=NR'$, -S(O)R', $-S(O)_2R'$, $-S(O)_2NR'R"$, $-N_3$, $-CH(Ph)_2$, perfluoro(C_1-C_4)alkoxy, and perfluoro(C_1-C_4)alkyl, in a number ranging from zero to the total number of open valences on the aromatic ring system; and where R', R" and R"' are independently selected from hydrogen, (C_1-C_8)alkyl and heteroalkyl, unsubstituted aryl and heteroaryl, (unsubstituted aryl)-(C_1-C_4)alkyl, and (unsubstituted aryl)oxy-(C_1-C_4)alkyl.

Two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-T-C(O)-(CH_2)_q-U-$, wherein T and U are independently -NH-, -O-, $-CH_2-$ or a single bond, and q is an integer of from 0 to 2. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-A-(CH_2)_r-B-$, wherein A and B are independently $-CH_2-$, -O-, -NH-, -S-, -S(O)-, $-S(O)_2-$, $-S(O)_2NR'-$ or a single bond, and r is an integer of from 1 to 3. One of the single bonds of the new ring so formed may optionally be replaced with a double bond. Alternatively, two of the substituents on adjacent atoms of the aryl or heteroaryl ring may optionally be replaced with a substituent of the formula $-(CH_2)_s-X-(CH_2)_t-$, where s and t are independently integers of from 0 to 3, and X is -O-, -NR'-, -S-, -S(O)-, $-S(O)_2-$, or $-S(O)_2NR'-$. The substituent R' in -NR'- and $-S(O)_2NR'-$ is selected from hydrogen or unsubstituted (C_1-C_6)alkyl.

As used herein, the term "heteroatom" is meant to include oxygen (O), nitrogen (N), sulfur (S) and silicon (Si).

The term "pharmaceutically acceptable salts" is meant to include salts of the active compounds which are prepared with relatively nontoxic acids or bases, depending on the particular substituents found on the compounds described herein. When compounds of the present invention contain relatively acidic functionalities, base addition salts can be obtained by contacting the neutral form of such compounds with a sufficient

amount of the desired base, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable base addition salts include sodium, potassium, calcium, ammonium, organic amino, or magnesium salt, or a similar salt. When compounds of the present invention contain relatively basic functionalities, acid addition salts can be obtained by contacting the neutral form of such compounds with a sufficient amount of the desired acid, either neat or in a suitable inert solvent. Examples of pharmaceutically acceptable acid addition salts include those derived from inorganic acids like hydrochloric, hydrobromic, nitric, carbonic, monohydrogencarbonic, phosphoric, monohydrogenphosphoric, dihydrogenphosphoric, sulfuric, monohydrogensulfuric, hydriodic, or phosphorous acids and the like, as well as the salts derived from relatively nontoxic organic acids like acetic, propionic, isobutyric, oxalic, maleic, malonic, benzoic, succinic, suberic, fumaric, mandelic, phthalic, benzenesulfonic, p-tolylsulfonic, citric, tartaric, methanesulfonic, and the like. Also included are salts of amino acids such as arginate and the like, and salts of organic acids like glucuronic or galactunoric acids and the like (see, for example, Berge, S.M., et al, "Pharmaceutical Salts", *Journal of Pharmaceutical Science*, 1977, *66*, 1-19). Certain specific compounds of the present invention contain both basic and acidic functionalities that allow the compounds to be converted into either base or acid addition salts.

The neutral forms of the compounds may be regenerated by contacting the salt with a base or acid and isolating the parent compound in the conventional manner. The parent form of the compound differs from the various salt forms in certain physical properties, such as solubility in polar solvents, but otherwise the salts are equivalent to the parent form of the compound for the purposes of the present invention.

In addition to salt forms, the present invention provides compounds which are in a prodrug form. Prodrugs of the compounds described herein are those compounds that readily undergo chemical changes under physiological conditions to provide the compounds of the present invention. Additionally, prodrugs can be converted to the compounds of the present invention by chemical or biochemical methods in an *ex vivo* environment. For example, prodrugs can be slowly converted to the compounds of the present invention when placed in a transdermal patch reservoir with a suitable enzyme or chemical reagent.

Certain compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms are equivalent to unsolvated forms and are intended to be encompassed within the scope of

the present invention. Certain compounds of the present invention may exist in multiple crystalline or amorphous forms. In general, all physical forms are equivalent for the uses contemplated by the present invention and are intended to be within the scope of the present invention.

Certain compounds of the present invention possess asymmetric carbon atoms (optical centers) or double bonds; the racemates, diastereomers, geometric isomers and individual isomers are all intended to be encompassed within the scope of the present invention.

The compounds of the present invention may also contain unnatural proportions of atomic isotopes at one or more of the atoms that constitute such compounds. For example, the compounds may be radiolabeled with radioactive isotopes, such as for example tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). All isotopic variations of the compounds of the present invention, whether radioactive or not, are intended to be encompassed within the scope of the present invention.

General

A number of arylsulfonamides have recently been described for the treatment of disorders and conditions arising from abnormal cell proliferation and from elevated plasma cholesterol levels. See, for example, PCT publications WO 97/30677, WO 98/05315 and WO 99/10320. Representative of this new class of anticancer agents are the pentafluorobenzenesulfonamides described in WO 98/05315. These agents are thought to exert their effect by binding to β-tubulin and disrupting microtubule formation. See, Medina *et al.*, Bioorganic & Med. Chem. Letters, 8(19):2653-56 (1998).

Still other pentafluorobenzenesulfonamides have been described in co-pending applications Ser. Nos. 60/090,681 filed June 25, 1998 and 09/336,062 filed June 18, 1999; Ser. Nos. 60/093,570 filed July 20, 1998 and 09/353,976 filed July 15, 1999; and Ser No. 60/100,888 filed September 23, 1998.

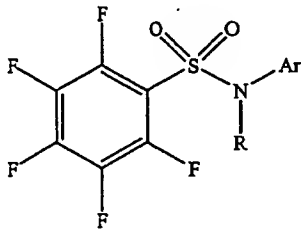
Clinical trials are in progress to evaluate the pentafluorobenzene-sulfonamide class of compounds for the treatment of cancer, both alone and in combination with other agents. The concept of combination therapy is well exploited in current medical practice. Treatment of a pathology by combining two or more agents that target the same pathogen or biochemical pathway sometimes results in greater efficacy and diminished side effects relative to the use of the therapeutically relevant dose of each

agent alone. In some cases, the efficacy of the drug combination is *additive* (the efficacy of the combination is approximately equal to the sum of the effects of each drug alone), but in other cases the effect can be *synergistic* (the efficacy of the combination is greater than the sum of the effects of each drug given alone). In real medical practice, it is often quite difficult to determine if drug combinations are additive or synergistic.

Description of the Embodiments

Compositions

In one aspect, the present invention provides compositions comprising an antineoplastic agent and a compound having the formula:



(I)

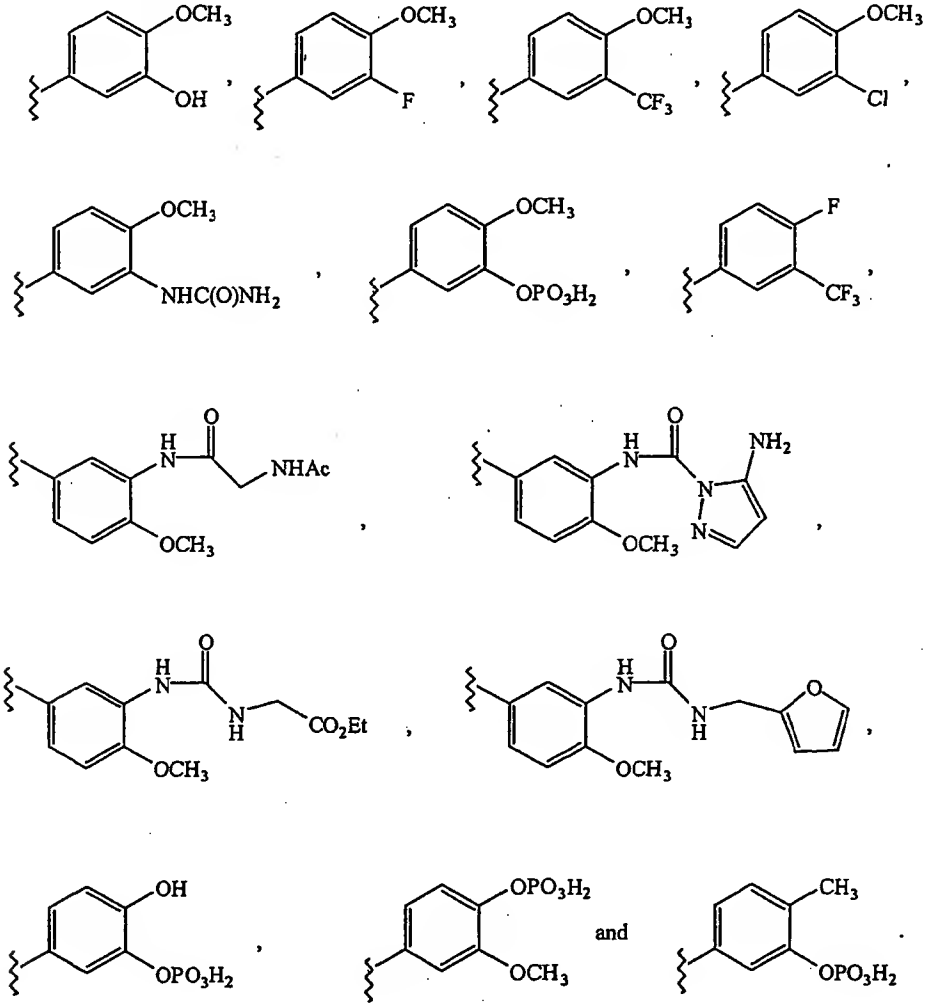
or a pharmaceutically acceptable salt thereof.

In the formula above, the letter R represents a hydrogen, substituted or unsubstituted (C_1-C_{10})alkyl, or substituted or unsubstituted (C_3-C_6)alkenyl. The symbol Ar represents a substituted or unsubstituted aryl group or a substituted or unsubstituted heteroaryl group.

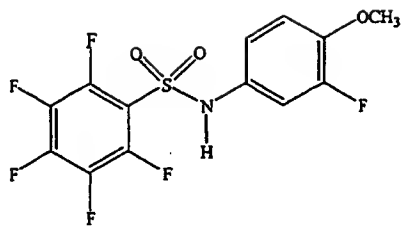
In preferred embodiments, R represents a hydrogen or a substituted or unsubstituted (C_1-C_4)alkyl group, more preferably hydrogen, methyl or ethyl.

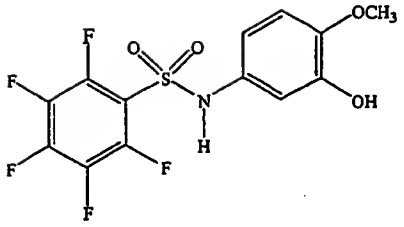
Also preferred are those embodiments in which Ar represents a substituted aryl or substituted heteroaryl group, preferably those having a single ring (*e.g.*, substituted phenyl, substituted pyridyl and substituted pyrimidyl). Particularly preferred embodiments are those in which Ar is substituted phenyl. For those embodiments in which Ar is substituted phenyl, the substituents will typically be present in a number of from one to three. Preferred substituents are selected from -halogen, -OR', -OC(O)R', -NR'R", -SR', -R', -CN, -NO_2, -CO_2R', -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(O)R', -NR"$C(O)_2$R', -NR'-C(O)NR"R"', -NH-$C(NH_2)$=NH, -NR'$C(NH_2)$=NH, -NH-$C(NH_2)$=NR', perfluoro(C_1-C_4)alkoxy, and perfluoro(C_1-C_4)alkyl, where R', R" and R"' are independently selected from hydrogen, (C_1-C_4)alkyl, unsubstituted aryl and

heteroaryl, (unsubstituted aryl)-(C_1-C_4)alkyl, and (unsubstituted aryl)oxy-(C_1-C_4)alkyl. Particularly preferred substituents are halogen, (C_1-C_4)alkyl, -OR', -OC(O)R', -NR'R", -CO_2R', -CONR'R", -C(O)R', -OC(O)NR'R", -NR"C(O)R', -NR"C(O)$_2$R', -NR'-C(O)NR"R"', perfluoro(C_1-C_4)alkoxy, and perfluoro(C_1-C_4)alkyl, in which R', R" and R"' are hydrogen or (C_1-C_4)alkyl. Still further preferred are those embodiments in which Ar is selected from:

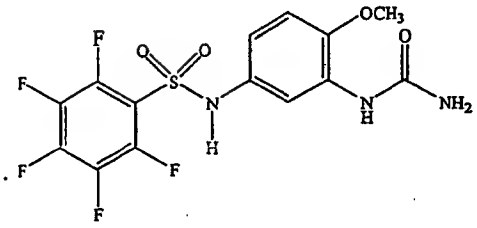


In the most preferred embodiments of the invention, the pentafluorobenzenesulfonamide compound used in the composition is selected from:





and



The compositions of the present invention will further comprise an antineoplastic agent. Suitable antineoplastic or antiproliferative agents include, but are not limited to, DNA-alkylating agents (e.g., cyclophosphamide, BCNU, busulfan and temozolamide), antimetabolites, antifolates and other inhibitors of DNA synthesis (e.g., methotrexate, 5-fluorouracil, gemcitabine), microtubule disruptors (e.g., vincristine, vinorelbine, paclitaxel, docetaxel), DNA intercalators (e.g., doxorubicin, daunomycin), hormone agents (e.g., tamoxifen, flutamide), topoisomerase I/II inhibitors and DNA repair agents (e.g., hydroxyurea, camptothecin, etoposide), growth factor receptor kinase inhibitors (e.g., AG1478 and AG1296), biological response modifiers (including cytokines such as interferon α and growth factor inhibitors), antiangiogenic and antivascular agents (e.g., combretastatin A-4), and other agents such as immunoconjugates (e.g., trasuzamab) and antisense oligonucleotides.

Thus, in one embodiment of the present invention, the composition comprises a pentafluorobenzenesulfonamide as defined herein and an antineoplastic agent selected from the group consisting of DNA-alkylating agents, antimetabolites, antifolates and other inhibitors of DNA synthesis, microtubule disruptors, DNA intercalators, hormone agents, topoisomerase I/II inhibitors, DNA repair agents, growth factor receptor kinase inhibitors, biological response modifiers, antiangiogenic and antivascular agents, immunoconjugates and antisense oligonucleotides.

In another embodiment, the composition comprises a pentafluorobenzenesulfonamide as defined herein and an antineoplastic agent selected from the group consisting of cyclophosphamide, BCNU (carmustine), busulfan, temozolomide, UFT, capecitabine, gemcitabine, cytarabine, improsulfan, piposulfan,

benzodepa, carboquone, meturedepa, uredepa, altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, trimethylolmelamine, chlorambucil, estramustine, ifosfamide, novembrichin, prednimustine, uracil mustard, dacarbazine, fluorouracil, methotrexate, mercaptopurine, thioguanine, vinblastine, vincristine, vinorelbine, vindesine, etoposide, teniposide, daunorubicin, doxorubicin, epirubicin, mitomycin, dactinomycin, daunomycin, plicamycin, bleomycin, L-asparaginase, camptothecin, hydroxyurea, procarbazine, mitotane, aminoglutethimide, tamoxifen, flutamide, mitoxantrone, paclitaxel, docetaxol, and thiotepa.

In preferred embodiments, the antineoplastic agent is gemcitabine or paclitaxel.

As noted above, in the most preferred embodiments of the present invention, the pentafluorobenzenesulfonamide compound used in the compositions is selected from Compound 1, Compound 2, and Compound 3 (see Figure 3). While an understanding of the mechanism by which these compounds are metabolized is not necessary in order to practice the present invention, it is believed that glutathione conjugation plays a major role. Some preferred embodiments of the invention entail the use of compositions comprising Compound 1, Compound 2, or Compound 3 with an antineoplastic agent whose metabolism also is dependent, at least in part, on the formation of a glutathione conjugate (which may include, e.g., BCNU, cyclophosphamide, and thiotepa). Determination of glutathione metabolism can be accomplished according to standard methods known to those of skill in the art (see, e.g., Mannervik and Widersten in ADV. IN DRUG METAB. IN MAN, G.M. Pacifici and G.N. Fracchis, eds., European Commission, Luxemburg: 407-459 (1995), using glutathione transferases available from commercial sources such as PanVera, product nos. P2175, P2192 and P2177, and Research Diagnostics). Enhanced efficacy may be observed with such combinations due to competition for glutathione metabolism. Depending on the agents involved, this may result in depletion of glutathione levels, delayed metabolism of one or both agents, and increased exposure of the malignant tissue to one or more of the composition's active components.

Methods of Treating Proliferative Disorders

The present invention provides, in another aspect, methods for the treatment of proliferative disorders. In one embodiment, treatment is carried out using a

composition comprising each of the two agents described above. In another embodiment, treatment comprises separate administration of one or more antineoplastic agents and a pentafluorophenylsulfonamide of formula I.

i. combination composition

In this embodiment of the invention, a composition of two or more agents (described above) is administered to a patient in need of treatment. The amount of each agent will typically be less than an amount that would produce a therapeutic effect if administered alone. The precise method of administration will depend on the patient and the judgment of the clinician, but will preferably be intravenous.

ii. compositions used sequentially (administer each separately)

In this embodiment of the invention, conventional protocols are described for the administration of an antineoplastic agent and compound 1 (as representative of the compounds of formula I). One of skill in the art will understand that various changes can be made by the clinician, depending on the particular agents selected for use and the routes and timing of administration. Thus, the present invention contemplates that the antineoplastic agent and the compounds of formula I can be administered sequentially on the same day, on concurrent days, or up to about 4 weeks apart.

The antineoplastic agent is preferably administered with a single intravenous infusion on day one of compound 1 administration period about four hours after the first day's administration of compound 1. To maintain sufficient hydration, one liter of normal saline with 20 meq KCl/L and 1 gm of magnesium sulfate, at a rate of about 250 ml/hour is administered prior to and after the infusion. Additional fluid may be given to maintain adequate urine output.

The treatment cycle may be continued until a clinical response is achieved or until intolerable side effects are encountered. The dosages of compound 1 and/or antineoplastic agent may be increased with each new treatment cycle, provided intolerable side effects are not encountered. The dosages may also be decreased if intolerable side effects are encountered. It is presently preferred to gradually adjust the dosage of compound 1 while holding the antineoplastic agent dosage constant.

As alluded to previously, certain preferred embodiments of the present invention entail combination therapy involving a pentafluorobenzenesulfonamide compound selected from Compound 1, Compound 2, and Compound 3 (see Figure 3) and at least one other antineoplastic agent, wherein metabolism of the other antineoplastic

agent(s) is dependent, at least in part, on the formation of a glutathione conjugate. In such embodiments, the order of administration may be especially important; that is, the order of administration may result in enhanced efficacy while minimizing adverse effects. In some preferred embodiments, it is preferable to administer Compound 1, Compound 2 or Compound 3 prior to the other antineoplastic agent, while in other preferred embodiments it is advantageous to co-administer the agents.

A common, but tolerable side effect of antineoplastic agent is nausea and vomiting. This can be alleviated by administering an anti-emetic (e.g., Ondansetron®, Granisetron®, Decadron®, Haldol®, Benadryl®, Ativan® and the like).

Of course, other forms of administration of both active ingredients, as they become available, are contemplated, such as by nasal spray, transdermally, by suppository, by sustained release dosage form, by IV injection, etc. Any form of administration will work so long as the proper dosages are delivered without destroying the active ingredient.

The effectiveness of treatment may be determined by controlled clinical trials. Patients having cancer with measurable or evaluable tumors will be included in the study. A measurable tumor is one that can be measured in at least two dimensions such as a lung tumor surrounded by aerated lung, a skin nodule, or a superficial lymph node. An evaluable tumor in one that can be measured in one dimension such as a lung tumor not completely surrounded by aerated lung or a palpable abdominal or soft tissue mass that can be measured in one dimension. Tumor markers which have been shown to be highly correlated with extent of disease will also be considered to provide an evaluable disease, such as PSA for prostate cancer, CA-125 for ovarian cancer, CA-15-3 for breast cancer, etc.

The tumor will be measured or evaluated before and after treatment by whatever means provides the most accurate measurement, such as CT scan, MRI scan, Ultrasonography, etc. New tumors or the lack thereof in previously irradiated fields can also be used to assess the anti-tumor response. The criteria for evaluating response will be similar to that of the WHO Handbook of Reporting Results of Cancer Treatment, WHO Offset Publication 1979, 49-World Health Organization, Geneva. The following results are defined for uni- and bi-dimensionally measurable tumors.

Complete response: Complete disappearance of all clinically detectable malignant disease determined by two observations not less than four weeks apart.

Partial Response: (a) for bidimensionally measurable tumors, a decrease of

at least 50% in the sum of the products of the largest perpendicular diameters of all measurable tumors as determined by two observations not less than four weeks apart. (b) for unidimensionally measurable tumors, a decrease by at least 50% in the sum of the largest diameters of all tumors as determined by two observations not less than four weeks apart. In cases where the patient has multiple tumors, It is not necessary for all tumors to have regressed to achieve a partial response as defined herein, but no tumor should have progressed and no new tumor should appear.

Stable disease: (a) for bidimensionally measurable tumors, less than a 50% decrease to less than a 25% increase in the sum of the products of the largest perpendicular diameters of all measurable tumors. (b) for unidimensionally measurable tumors, less than a 50% decrease to less than a 25 % increase in the sum of the diameters of all tumors. For (a) and (b) no new tumors should appear.

No clinical response, i.e. progressive disease in defined as an increase of more than 50% in the product of the largest perpendicular diameters for at least one bidimensionally measurable tumor, or an increase of more than 25% in measurable dimension of at least one unidimensionally measurable tumor.

Of course elimination or alleviation of other known signs or symptoms of cancer, especially those listed previously can also be used to evaluate the effectiveness of this invention.

The cancers should be evaluated, i.e. tumors measured, etc., no more than 14 days before the start of the treatment. These cancers should be reevaluated about 28 days after day 1 of administration of the first dose of compound 1 and antineoplastic agent. Twenty eight days after this initial administration another administration period may be performed, and evaluations performed 28 days after the start of this second cycle. The treatment cycles may be continued until a clinical response is achieved or unacceptable toxicity is encountered.

Another aspect of this invention is the treatment of cancer with reduced side effects normally associated with an antineoplastic agent. This objective can be achieved by administration of lower doses of the two active ingredients or by shorter duration of dosing brought about by the synergistic effect of the combination.

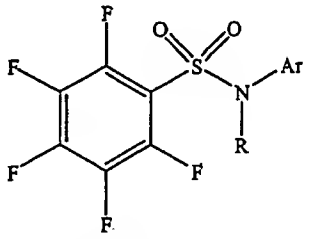
EXAMPLES

Figures 1 and 2 illustrate the effect achieved by combining a pentafluorobenzenesulfonamide with gemcitabine or with paclitaxel.

All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were specifically and individually indicated to be incorporated by reference. Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to those of ordinary skill in the art in light of the teachings of this invention that certain changes and modifications may be made thereto without departing from the spirit or scope of the appended claims.

WHAT IS CLAIMED IS:

1. A composition for the treatment of proliferative disorders, comprising an antineoplastic agent and a compound having the formula:



and pharmaceutically acceptable salts thereof;

wherein

R is a member selected from the group consisting of hydrogen and substituted or unsubstituted (C_1-C_{10})alkyl; and

Ar is a member selected from the group consisting of substituted or unsubstituted aryl and substituted or unsubstituted heteroary

2. A composition in accordance with claim 1, wherein said antineoplastic agent is selected from the group consisting of DNA-alkylating agents, antimetabolites, antifolates and other inhibitors of DNA synthesis, microtubule disruptors, DNA intercalators, hormone agents, topoisomerase I/II inhibitors, DNA repair agents, growth factor receptor kinase inhibitors, biological response modifiers, antiangiogenic and antivascular agents, immunoconjugates and antisense oligonucleotides.

3. A composition in accordance with claim 1, wherein said antineoplastic agent is selected from the group consisting of cyclophosphamide, BCNU, busulfan, temozolomide, UFT, capecitabine, gemcitabine, cytarabine, improsulfan, piposulfan, benzodepa, carboquone, meturedepa, uredepa, altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, trimethylolmelamine, chlorambucil, estramustine, ifosfamide, novembrichin, prednimustine, uracil mustard, dacarbazine, fluorouracil, methotrexate, mercaptopurine, thioguanine, vinblastine, vincristine, vinorelbine, vindesine, etoposide, teniposide, daunorubicin, doxorubicin, epirubicin, mitomycin, dactinomycin, daunomycin, plicamycin, bleomycin, L-asparaginase, camptothecin, hydroxyurea, procarbazine, mitotane, aminoglutethimide, tamoxifen, flutamide, mitoxantrone, paclitaxel, docetaxol, and thiotepa.

4. A composition in accordance with claim 1, wherein said antineoplastic agent is selected from the group consisting of doxorubicin, daunorubicin, gemcitabine and paclitaxel.

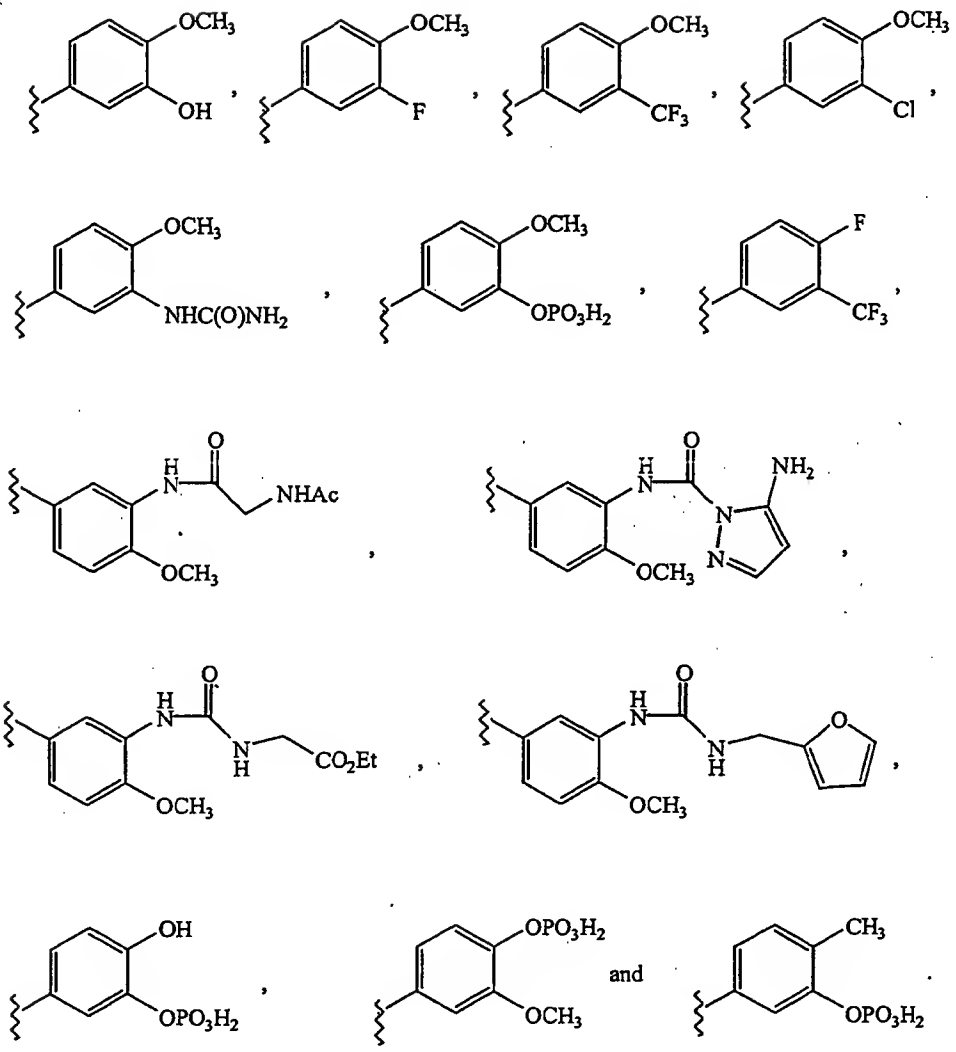
5. A composition in accordance with claim 1, wherein said antineoplastic agent is gemcitabine or paclitaxel.

6. A composition in accordance with claim 1, wherein R is hydrogen or unsubstituted (C_1-C_4)alkyl.

7. A composition in accordance with claim 1, wherein Ar is a substituted phenyl group.

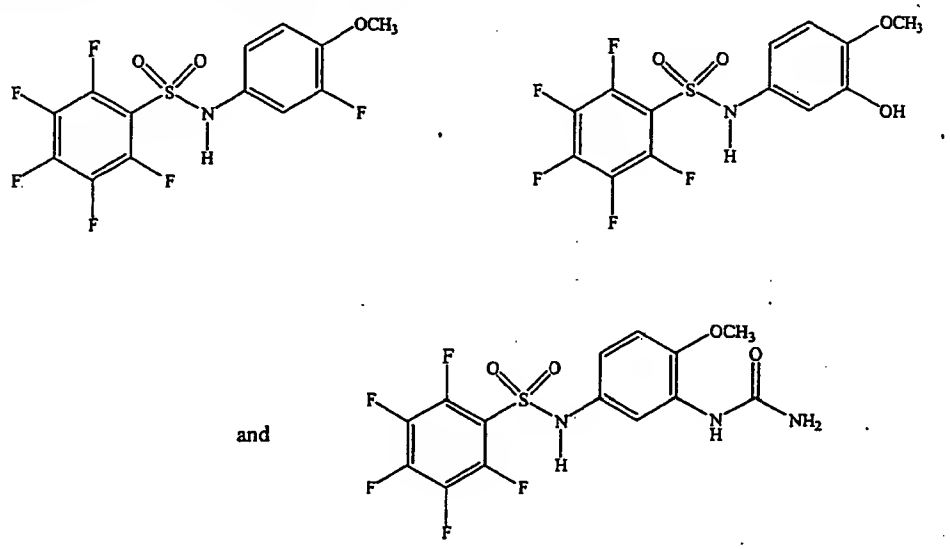
8. A composition in accordance with claim 7, wherein said substituents on said phenyl group are selected from the group consisting of halogen, (C_1-C_4)alkoxy, (C_1-C_4)alkyl, -OPO_3H_2,

9. A composition in accordance with claim 8, wherein Ar represents a member selected from the group consisting of



and

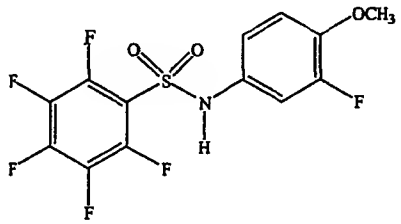
10. A composition in accordance with claim 1, wherein said compound is selected from the group consisting of:

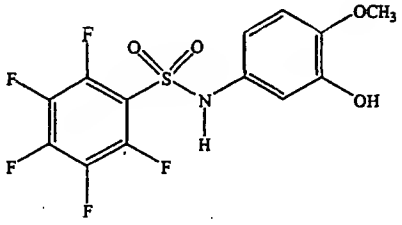


and

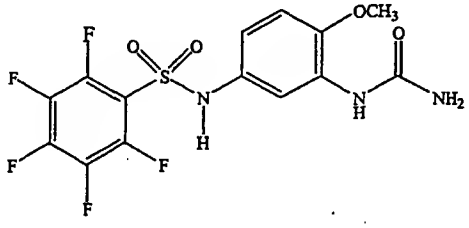
11. A method for the treatment of a proliferative disorder, comprising administering to a subject in need of such treatment an effective amount of a composition of claim 1.

12. A. method in accordance with claim 11, wherein said compound is selected from the group consisting of:





and



13. A method in accordance with claim 12, wherein said antineoplastic agent is selected from the group consisting of DNA-alkylating agents, antimetabolites, antifolates and other inhibitors of DNA synthesis, microtubule disruptors, DNA intercalators, hormone agents, topoisomerase I/II inhibitors, DNA repair agents, growth factor receptor kinase inhibitors, biological response modifiers, antiangiogenic and antivascular agents, immunoconjugates and antisense oligonucleotides.

14. A method in accordance with claim 12, wherein said antineoplastic agent is selected from the group consisting of cyclophosphamide, BCNU, busulfan, temozolomide, UFT, capecitabine, gemcitabine, cytarabine, improsulfan, piposulfan, benzodepa, carboquone, meturedepa, uredepa, altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, trimethylolmelamine, chlorambucil, estramustine, ifosfamide, novembrichin, prednimustine, uracil mustard, dacarbazine, fluorouracil, methotrexate, mercaptopurine, thioguanine, vinblastine,

vincristine, vinorelbine, vindesine, etoposide, teniposide, daunorubicin, doxorubicin, epirubicin, mitomycin, dactinomycin, daunomycin, plicamycin, bleomycin, L-asparaginase, camptothecin, hydroxyurea, procarbazine, mitotane, aminoglutethimide, tamoxifen, flutamide, mitoxantrone, paclitaxel, docetaxol, and thiotepa.

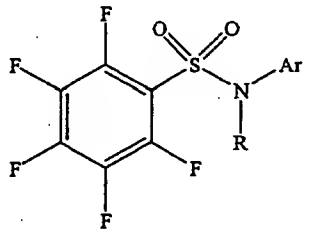
15. A method in accordance with claim 12, wherein said antineoplastic agent is selected from the group consisting of doxorubicin, daunorubicin, gemcitabine and paclitaxel.

16. A method in accordance with claim 12, wherein said antineoplastic agent is gemcitabine or paclitaxel.

17. A method for the treatment of a proliferative disorder, comprising administering to a subject in need of such treatment:

i) a first amount of an antineoplastic agent; and

ii) a second amount of a compound of formula:



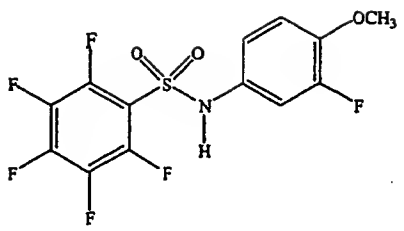
and pharmaceutically acceptable salts thereof; wherein

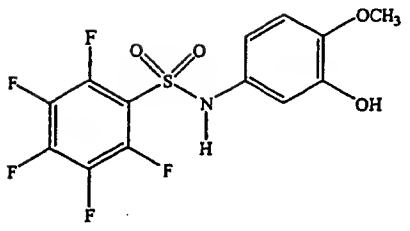
R is a member selected from the group consisting of hydrogen and substituted or unsubstituted (C_1-C_{10})alkyl; and

Ar is a member selected from the group consisting of substituted or unsubstituted aryl and substituted or unsubstituted heteroaryl;

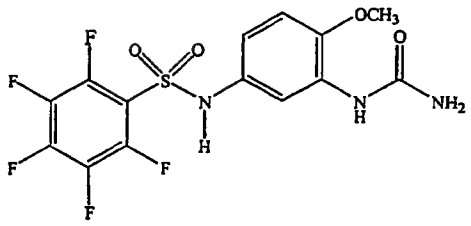
wherein said first amount and said second amount, in combination, are effective to treat said proliferative disorder

18. A method in accordance with claim 17, wherein said compound is selected from the group consisting of





and



19. A method in accordance with claim 18, wherein said antineoplastic agent is selected from the group consisting of DNA-alkylating agents, antimetabolites, antifolates and other inhibitors of DNA synthesis, microtubule disruptors, DNA intercalators, hormone agents, topoisomerase I/II inhibitors, DNA repair agents, growth factor receptor kinase inhibitors, biological response modifiers, antiangiogenic and antivascular agents, immunoconjugates and antisense oligonucleotides.

20. A method in accordance with claim 18, wherein said antineoplastic agent is selected from the group consisting of cyclophosphamide, BCNU, busulfan, temozolomide, UFT, capecitabine, gemcitabine, cytarabine, improsulfan, piposulfan, benzodepa, carboquone, meturedepa, uredepa, altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, trimethylolmelamine, chlorambucil, estramustine, ifosfamide, novembrichin, prednimustine, uracil mustard, dacarbazine, fluorouracil, methotrexate, mercaptopurine, thioguanine, vinblastine, vincristine, vinorelbine, vindesine, etoposide, teniposide, daunorubicin, doxorubicin, epirubicin, mitomycin, dactinomycin, daunomycin, plicamycin, bleomycin, L-asparaginase, camptothecin, hydroxyurea, procarbazine, mitotane, aminoglutethimide, tamoxifen, flutamide, mitoxantrone, paclitaxel, docetaxol, and thiotepa.

21. A method in accordance with claim 18, wherein said antineoplastic agent is selected from the group consisting of doxorubicin, daunorubicin, gemcitabine and paclitaxel.

22. A method in accordance with claim 18, wherein said antineoplastic agent is gemcitabine or paclitaxel.

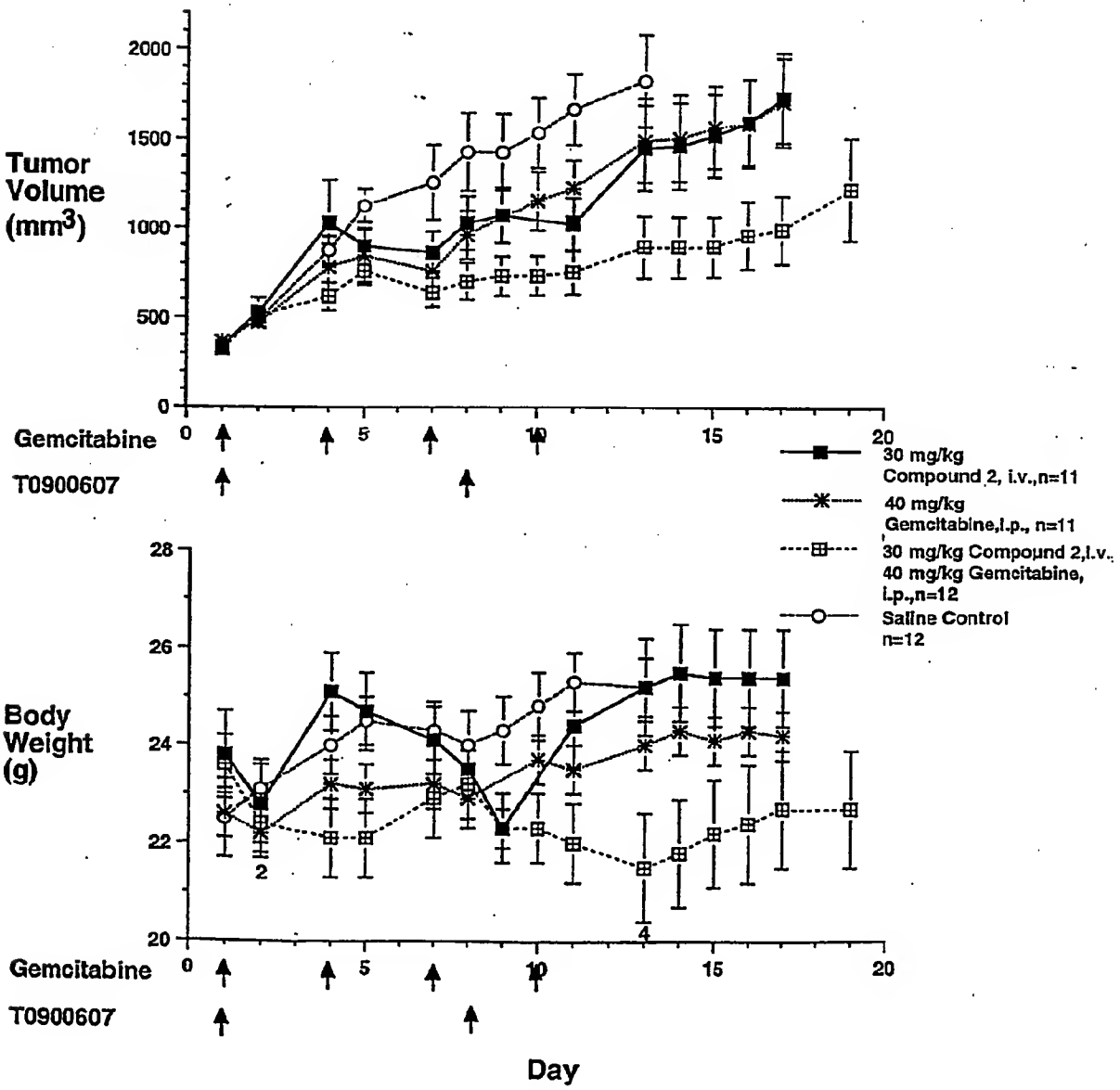
23. A method in accordance with claim 18, wherein said antineoplastic agent is administered prior to said compound.

24. A method in accordance with claim 18, wherein said antineoplastic agent is administered after said compound.

25. A method in accordance with claim 18, wherein said antineoplastic agent is administered simultaneously with said compound.

FIGURE 1

Efficacy of Compound 2 or Gemcitibine Either Alone or in Combination Against MX-1 Human Mammary Tumor Xenografts in Athymic Nude Mice



Arrow indicates dose administration. Results are expressed as the mean ± SEM.

FIGURE 2

Efficacy of Compound 2 or Paclitaxel Either Alone or in Combination Against MX-1 Human Mammary Tumor Xenografts in Athymic Nude Mice

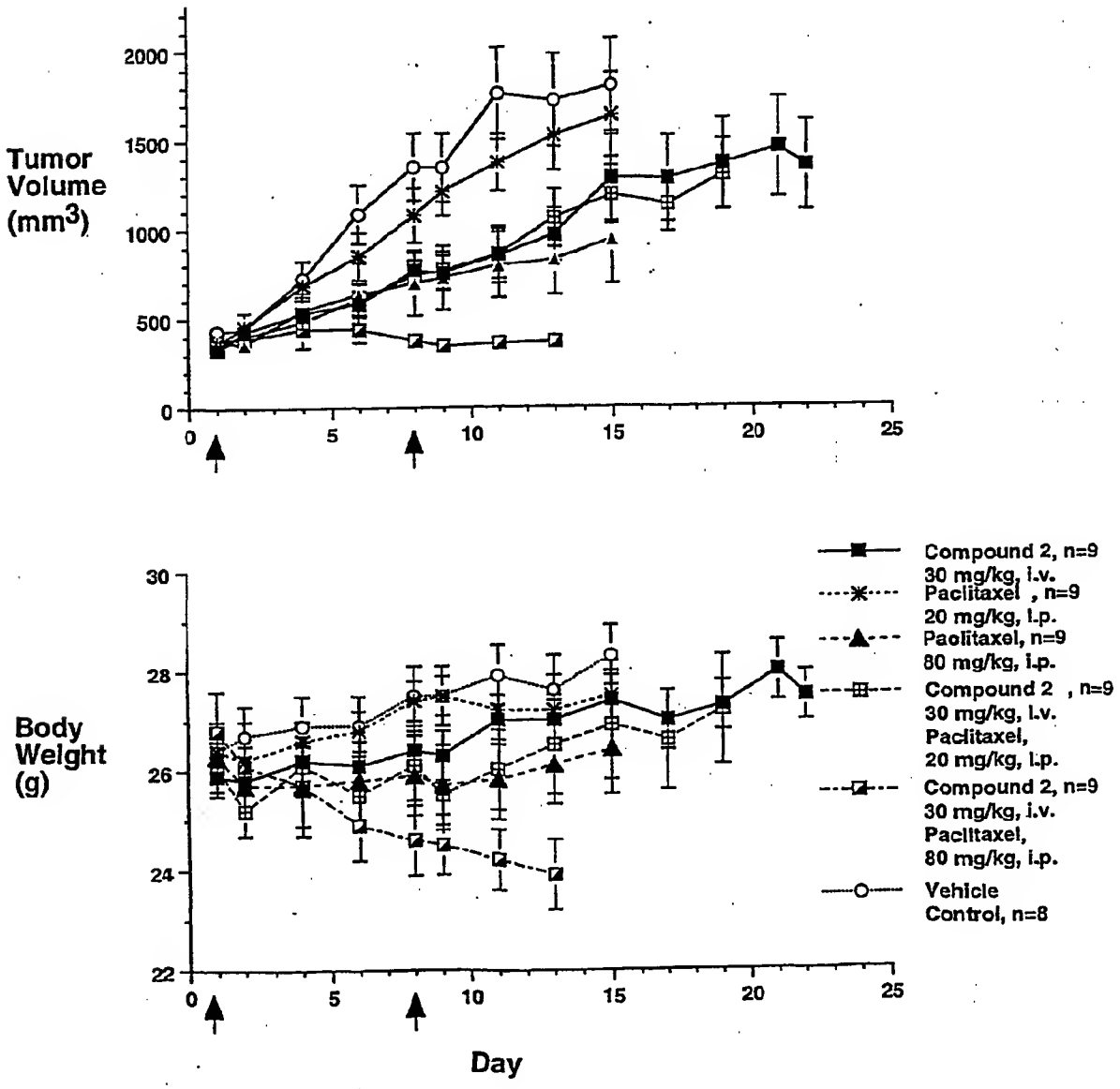
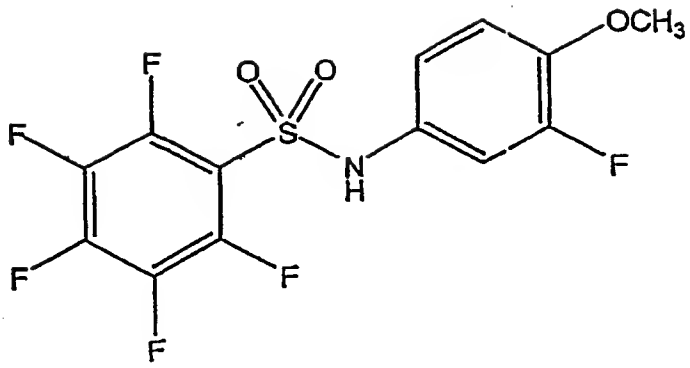
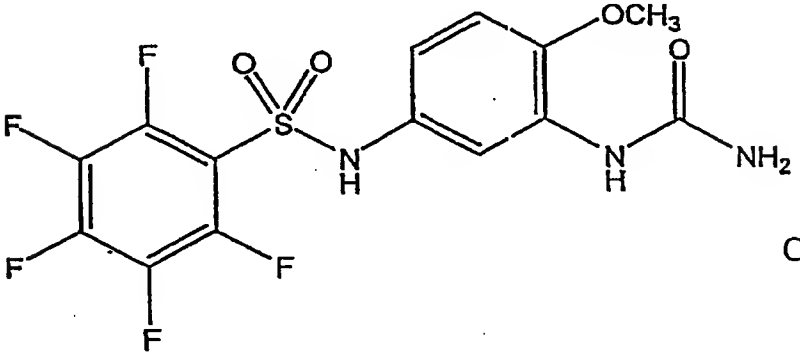


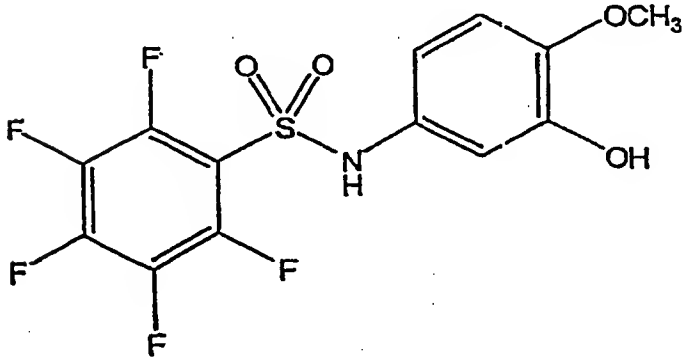
FIGURE 3



COMPOUND 1
(sodium salt)



COMPOUND 2



COMPOUND 3

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(71) Applicant *(for all designated States except US)*: TULARIK INC. [US/US]; Two Corporate Drive, South San Francisco, CA 94080 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: SCHWENDNER, Susan [US/US]; 2000 Crystal Springs Road, #7-05, San Bruno, CA 94066 (US). TIMMERMANS, Pieter [NL/US]; 850 Hillcrest Drive, Redwood City, CA 94062 (US). WALLING, Jacqueline [GB/US]; 2710 Easton Drive, Burlingame, CA 94010 (US).

(74) Agents: KEZER, William, B. et al.; Townsend and Townsend and Crew LLP, Two Embarcadero Center, Eighth Floor, San Francisco, CA 94111 (US).

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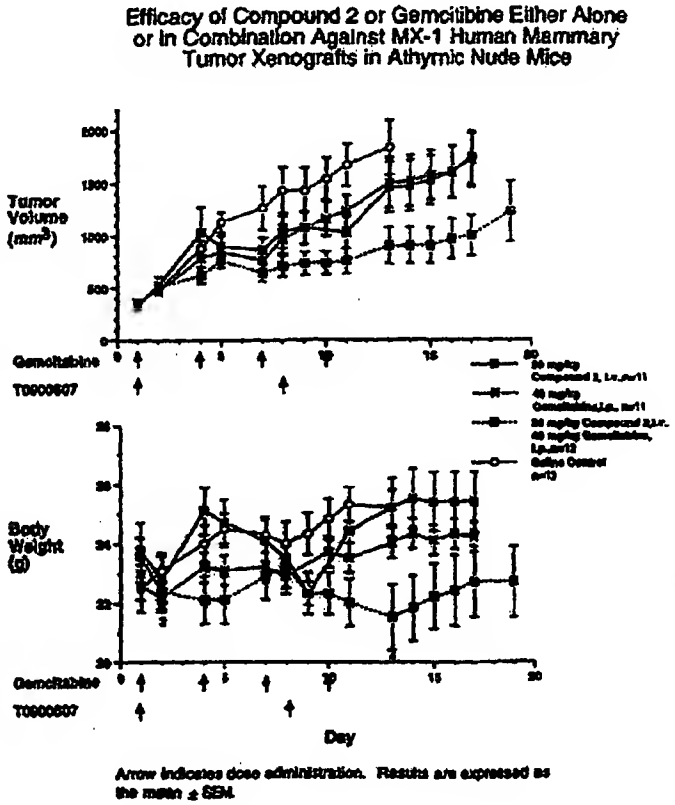
[Continued on next page]

(54) Title: COMBINATION THERAPY USING PENTAFLUOROBENZENESULFONAMIDES AND ANTINEOPLASTIC AGENTS



(57) Abstract: Combination therapies are provided for the treatment of proliferative disorders which use a pentafluorobenzenesulfonamide of formula I and an antineoplastic agent such as gemcitabine or paclitaxel.

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Published:
— *with international search report*

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6 September 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/51136

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/415; A01N 43/38; C07D 231/56; C07C 303/00; C07C 307/00
US CL : 514/403, 415, 518, 602, 604; 548/361.1, 469; 558/56, 61; 564/90, 92

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/403, 415, 518, 602, 604; 548/361.1, 469; 558/56, 61; 564/90, 92

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98/05315 A1 (TULARIK, INC.) 12 February 1998 (12.2.1998), see entire document, especially page 29, lines 21 and 22, and Examples 6 and 7 on page 33.	1-25
Y	US 5,880,151 A (MEDINA et al) 09 March 1999 (9.3.1999), see entire document, especially column 23, lines 25-55.	1-25
Y	US 6,121,304 A (FLYGARE et al) 19 September 2000 (19.9.2000), see entire document, especially column 24, lines 1-35.	1-25
Y	MEDINA et al. Novel antineoplastic agents with efficacy against multidrug resistant tumor cell lines. Bioorg. Med. Chem. Lett. 1998. Vol. 8, No. 9, pages 2653-2656, see entire document, especially abstract.	1-25

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"B" earlier application or patent published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
18 March 2002 (18.03.2002)	20 MAY 2002
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer Richard Schnizer Telephone No. (703) 308-0196

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/51136

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
Please See Continuation Sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US01/51136

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-10, drawn to compositions for the treatment of proliferative disorders.

Group II, claim(s) 11-25, drawn to methods of treating proliferative disorders.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The technical feature linking the two groups cannot be a special technical feature under PCT Rule 13.2 because the technical feature fails to make a contribution over the prior art.
The technical feature linking groups I and II is a pentafluorosulfonamide compound in which the sulfonamide nitrogen is substituted with an aryl group and either a hydrogen or an alkyl group. However, such compounds were known in the prior art. See e.g. WO 98/05315, US Patents 5,880,151, and 6,121,304, and Medina et al (Bioorg. Med. Chem. Lett. (1988) Vol. 8, No. 19, pages 2653-2656.
Because the technical feature linking the inventions was known in the prior art, it cannot be a special technical feature under PCT Rule 13.2, and the claimed inventions lack unity under PCT Rule 13.1.

This application contains claims directed to more than one species of the generic invention. These species are deemed to lack unity of invention because they are not so linked as to form a single general inventive concept under PCT Rule 13.1.
The species are as follows: the antineoplastic agents listed in claims 2, 3, 14, and 20.

The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: The combination of an antineoplastic agent and the pentafluorosulfonamide does not relate to a single general inventive concept under PCT Rule 13.1 because it fails to make a contribution over the prior art. WO 98/05315 teaches this combination. See e.g. page 29, lines 21 and 22; and Examples 6 and 7 on page 33.

However, an election will not be required as the species are considered to be obvious in view of each other.

Continuation of B. FIELDS SEARCHED Item 3:
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WEST

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(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
11 July 2002 (11.07.2002)

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(71) Applicant and
(72) Inventor: SHANAHAN-PRENDERGAST, Elisabeth [IE/IE]; Baybush, Straffen, County Kildare (IE).

(74) Agent: MACLACHLAN & DONALDSON; 47 Merrion Square, Dublin 2 (IE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 02/053138 A2

(54) Title: TREATMENT FOR INHIBITING NEOPLASTIC LESIONS

(57) Abstract: The invention discloses the use of incensole and/or furanogermacrens, derivatives metabolites and precursors thereof in the treatment of neoplasia, particularly resistant neoplasia and immundysregulatory disorders. These compounds can be administered alone or in combination with conventional chemotherapeutic, anti-rival, anti-parasite agents, radiation and/or surgery.

"Treatment for inhibiting neoplastic lesions"

The present invention relates to a method for the selective inhibition of neoplastic cells, for example for the treatment, inhibition or prevention of precancerous lesions, tumours, cancer growth or other neoplasias in mammals. This invention also relates to the use of the compounds of the present invention including incensole and/or furanogermacren, derivatives, metabolites, analogues, mimic molecules and to compositions containing the compounds of the present invention including incensole and/or furanogermacren, derivatives, metabolites, analogues, mimic molecules.

Cancer develops from changes in the DNA, or genetic material, of the body's cells, causing them to develop into precancerous lesions. Such lesions exhibit a strong tendency to develop into malignant tumours, or cancer. Such lesions include lesions of the breast (that can develop into breast cancer), lesions of the skin (that can develop into malignant melanoma or basal cell carcinoma), colonic adenomatous polyps (that can develop into colon cancer), and other such neoplasms.

Cancer may take years to develop. The process typically begins with some disruption to the DNA of a cell, the genetic code that directs the life of the cell. Many things, such as diet, tobacco, sun exposure or certain chemicals can cause such disruptions. Some cells will enter a precancerous phase, known as dysplasia. Some cells will also enter the state of *carcinoma in situ*, in which the cancer cells are restricted to a microscopic site and do not pose a great threat. Eventually, unless the body's own immune system takes care of the wayward cells either on its own or by being enhanced by specific chemicals, a tumour will develop. It may take as long as 30 years for a tumour to go through the entire process and become large enough to produce clinical symptoms.

Anyone can get cancer, including children, but it is most common in people over the age of 50. This year about 1.22 million people in the United States will be diagnosed with cancer (not including the more than 1 million annual cases of basal

and squamous-cell skin cancers.) About 563,000 people will die of cancer this year. Treatment for cancer has progressed rapidly over the last 30 years. Doctors generally prescribe three main treatments for cancer: surgery, radiation therapy, chemotherapy or a combination of these. Choosing a course of medical treatment depends largely on the cancer type, stage of progression, and location.

Surgery is generally advisable when physicians can safely remove the cancer from the body. In situations where the cancerous cells have spread, surgeons sometimes must remove large areas of healthy tissue along with the tumour to insure that no malignancy remains. In these cases, physicians remove lymph nodes from the tumour area because cancer can spread through nodes. However, unfortunately most cancers are discovered too late for surgical cure. In many cases, the patient does not experience symptoms until the cancer has progressed to a malignant stage.

Radiation therapy is used to destroy cancer cells. Ironically, radiation can *cause* and *destroy* cancer. Side effects of radiation therapy include radiation sickness, which are nausea and skin redness in the tumour area.

Chemotherapy uses poison drugs that take advantage of cancer cells' rapid growth and consumption of large amounts of nutrients. Chemotherapy side effects include nausea and temporary full or partial hair loss. Antimetabolites, one group of these drugs, work by mimicking the nutrients the body's cells consume. Physicians inject these drugs into the bloodstream, where they travel throughout the body, consumed by every cell. Rapidly growing cancerous cells consume much more of the poisonous drugs than do normal cells. As a result, the drugs destroy cancerous cells faster than normal cells. Cells reproduce by duplicating their genetic code, or DNA. Another group of chemotherapy drugs interferes with the duplication of DNA, so cells cannot reproduce. Chemotherapy drugs act on all the patient's cells -- the cancerous cells and the healthy cells. A physician's challenge is to administer the drugs to kill only the cancer cells, not the healthy cells. Side effects such as those immediately described prevent the long term or recurrent use of these drugs. Furthermore, there are an increasing number of effective drugs that can no longer be used due to resistance by the causative agent.

Researchers have refined these three cancer treatments (surgery, radiation therapy and chemotherapy) over the past 20 years. As a result, the survival rate among cancer patients has increased dramatically. But, the success of any treatment for cancer depends on how much the cancer has spread before treatment begins. Once cancer metastasises, or spreads into different areas of the body, treating it with surgery, radiation therapy or chemotherapy becomes more difficult. As the tumour mass increases and cancerous cells proliferate, the cancer may become resistant to any type of therapy medicine can provide.

Early cancer detection is critical to successful treatment. If physicians destroy tumours before they have had an opportunity to spread, a person with cancer has a much greater chance for survival.

The search for drugs useful for treating and preventing cancer is intensive. Indeed, much of the focus of cancer research today is on the prevention of cancer because chemotherapy for cancer itself is often not effective and has severe side effects. Cancer chemoprevention is important for recovered cancer patients whom retain a risk of cancer recurrence. Also, cancer chemoprevention is important for individuals who, have not yet had cancer, but have hereditary factors that place them at risk of developing cancer. With the development of new genetic screening technologies, it is easier to identify patients with high-risk genetic factors, whom would greatly benefit from chemopreventative drugs. Therefore finding such anti-cancer drugs that can be used for prolonged preventive use is of vital interest.

Unfortunately, most chemotherapeutic drugs have serious side effects that prohibit their long-term use, or use in otherwise healthy individuals with precancerous lesions. There side effects, which are a result of non-specific toxicity of the drugs, immunosuppression and other toxicities. For this reason there is a need to identify new drug candidates for therapy of patients with precancerous lesions that do not have such serious side effects in humans.

The in vitro anti-tumour activity of several natural products has recently been examined to identify new compounds that inhibit the cancer cells whilst having lower side effects, as described in US580925; USUS6051565; US6080741; US5578637; US5578637; US5663196; US5602184; US5817816; and US56077840

to list but a few. A new group of drugs, utilizing monoclonal antibodies, designed to affect only cancer cells, leaving healthy cells intact have been tested. US 5064823 discloses the anticancer activity of pentacyclic triterpenoid compounds which possess topoisomerase inhibitory activity. US 5876728 is directed to a composition for treating cancer that contains at least three herbal extracts. These previously described compounds are unrelated to the present invention.

However, despite these developments, there exists a continuing need for chemotherapeutic agents which inhibit tumour growth, especially solid tumour growth and which have an adequate therapeutic index to be effective for in vivo treatment.

The correlation between the compounds of the present invention, incensole and furanogermacren, derivatives, metabolites, analogues and/or mimic molecules and neoplasia was not recognised prior to the work of the applicant. Accordingly the following provides information on each of these topics.

The present invention is directed to a composition comprising one or more compound of the present invention described herein, their derivatives, metabolites, analogues and/or mimic molecules with pharmaceutical acceptable additives, diluents, carriers, excipients and pharmaceutical salts thereof.

The present invention is further directed to a pharmaceutical formulation comprising a composition as described herein and a pharmaceutically acceptable carrier thereof.

The present invention is further directed to the use of the pharmaceutical formulation for the manufacture of a medicament for treatment of a mammal suffering from a neoplasia comprising a pharmaceutical formulation as described herein.

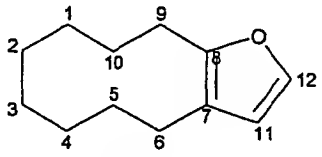
The present invention is also directed to the use of the pharmaceutical formulation for the manufacture of a medicament for sensitising a resistant neoplasia to subsequent therapy comprising administering to a patient in need thereof a therapeutically effective amount of composition as previously described.

The present invention is also directed to the use of a pharmaceutical formulation for the manufacture of a medicament for treatment of a mammal suffering from an immunodysregulatory condition comprising a composition as described herein to a subject.

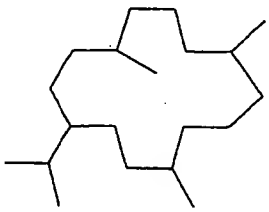
DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a composition comprising one or more compound of the present invention described herein, their derivatives, metabolites, analogues and/or mimic molecules with pharmaceutical acceptable additives, diluents, carriers, excipients and pharmaceutical salts thereof.

In one embodiment, the compounds of the present invention are selected from the group comprising:



Formula (1)



Formula (2)

wherein for Formula (1)

Bonds between carbons 9-10, 10-1, 1-2, 2-3,3-4, 4-5, 5-6, can be either single or double with the proviso that any two or more double bonds are separated by a single bond.

Compounds also include those containing epoxide rings formed between carbons 9-10, 10-1, 1-2, 2-3,3-4, 4-5 with the proviso that any two or more epoxide rings are separated by a single bond.

wherein for Formula (2)

the carbocyclic ring can have optionally up to 7 endocyclic/exocyclic double bonds with the proviso that any two or more double bonds are separated by single bonds;

Carbon atoms for Formula (1) or (2) can be singly or multiply substituted, optionally and independently by:

an oxo substituent, H, alkyl, aryl, a heterocyclic radical, halogen, alkoxycarbonyl (C1-C5) or carboxyl, hydroxyl, alkoxy (C1-C5), amido, alkyl amido (C1-C5), amino, mono and dialkyl amino (C1-C5), alkyl carbamoyl (C1-C5), thiol, alkylthio (C1-C5);

in addition substituents may form a spiro ring around the carbon atom to which they are attached or they can form fused or bridged rings to adjacent carbon atoms which may be saturated or unsaturated;

Substituents on the aryl or heterocyclic radical are selected from the group consisting essentially of: halogen, alkyl (C1-C5), hydroxyl, alkoxy (C1-C5), alkoxycarbonyl, (C1-C5), carboxyl, amido, alkyl amido (C1-C5), amino, mono and dialkyl amino (C1-C5),alkyl carbamoyl (C1-C5), thiol, alkyl thio (C1-C5) or benzenoid aryl thio, cyano, nitro, haloalkyl (C1-C5), alklsulfonyl (C1-C5), and sulfonate;

Two of such substituents can be part of a fused ring, which can be either saturated, or unsaturated, heterocyclic or carbo cyclic;

and natural amino acid substituents which may be attached to the compounds of formula (1) or (2) via an ester linkage to a hydroxyl group;

their derivatives, metabolites, analogues and/or mimic molecules with pharmaceutical acceptable additives, diluents, carriers and excipients and pharmaceutically acceptable salts thereof.

"Alkyl" as used herein means linked normal, secondary, tertiary or cyclic carbon atoms linear, branched or cyclic chains, saturated or unsaturated. The number of carbon atoms in an alkyl group or moiety is about 1 to about 20, unless otherwise specified, e.g. C1-10 alkyl means and alkyl moiety containing 1,2,3,4,5,6,7,8,9 or 10 carbon atoms. Substituents include but are not limited to halogen, alkyl (C1-C5), hydroxyl, alkoxy (C1-C5), alkoxycarbonyl, (C1-C5), carboxyl, amido, alkyl amido (C1-C5), amino, mono and dialkyl amino (C1-C5), alkyl carbamoyl (C1-C5), thiol, alkylthio (C1-C5) or benzenoid aryl.

"Aryl" as used herein refers to phenyl or naphthyl, or any optionally singly or multiply substituted benzenoid group (C6-C14). Substituents defined below.

"Heterocylic" are used refers to any 4, 5 or 6 membered, optionally substituted heterocyclic ring, saturated or unsaturated, containing 1-3 ring heteroatoms, the remaining ring atoms being carbon.

In one embodiment, substituents on the aryl or heterocyclic radical may include but are not limited to: halogen, alkyl (C1-C5), hydroxyl, alkoxy (C1-C5), alkoxycarbonyl, (C1-C5), carboxyl, amido, alkyl amido (C1-C5), amino, mono and dialkyl amino (C1-C5),alkyl carbamoyl (C1-C5), thiol, alkyl thio (C1-C5) or benzenoid aryl thio, cyano, nitro, haloalkyl (C1-C5), alklsulfonyl (C1-C5), and sulfonate.
Two of such substituents can be part of a fused ring, which can be either saturated, or unsaturated, heterocyclic or carbo cyclic.

In another embodiment, natural amino acid substituents which may be attached to the compounds of formula (1) or (2) via an ester linkage to a hydroxyl group.

In another embodiment, the compounds of the present invention are selected from the group comprising: incensole, incensole acetate, incensole oxide, incensole oxide acetate, isoincensole, isoincensole acetate, isoincensole oxide, octyl acetate, octanol, terpinyl acetate, bornyl acetate, trans-ver-benol, verbenone, menthadien-7-ol, terpinen-4-ol, trans-pinocarveol, carvone, borneol, farnesol, farnesene, β-

caryophyllene, humulene, β-cadinene, bergamotone, β-guaiene, β-ylangene, β-bourbonene, α-copaene, terpinene, myrcene, ρ-cymene, α- and β-phellandrene, α-thujene, cembrane-A, isocembrane, cembranol, cembranoids, cembranoid alcohols, furanogermacrens, furanogermacrene, germacrene, elemane, cadinene, guaiane, oplopane, eudsmane, echinodol, α-santalene, α-bisabolene, furanodiene, β-santalene, β-bergamotene, β-farnesene, β-bisabolene, SKB4, their derivatives, metabolites, analogues and/or mimic molecules with pharmaceutical acceptable additives, diluents, carriers and excipients and pharmaceutically acceptable salts thereof.

In another embodiment, the compounds of the present invention are selected from the group comprising at least one of: incensole, incensole acetate, incensole oxide, incensole oxide acetate, isoincensole, isoincensole acetate, isoincensole oxide, and/or at least one of the furanosesquiterpene furnogermacrens, their derivatives, metabolites, analogues and/or mimic molecules with pharmaceutical acceptable additives, diluents, carriers and excipients and pharmaceutically acceptable salts thereof.

In one embodiment, the composition is micronized. In accordance with the present invention, the expression "micronized" means that the composition has been micronized in accordance with any process for micronizing, a number of which are known in the art. The micronized particles preferably include a percentage of particles, which are of a diameter, which is about 10 microns, or less, preferably, 5 microns or less. For example, in a preferred aspect of the invention, at least 80% of the particles in a formulation of micronized particles have a diameter of less than 5 microns. An alternative to micronizing a compound is to solubilize the compound and put it into liposomes of appropriate size. The manufacture of liposomes and the insertion of active ingredients into such liposomes are well known in the art.

In another embodiment the composition is delivered to infected cells by incorporating the compounds of the present invention into liposomes or carbohydrate vehicles. In another embodiment, the composition is formulated into liposomes or carbohydrate vehicles.

In one embodiment, the liposomes or carbohydrate vehicles are specifically targeted to tumours by covalently attaching a monoclonal antibody directed to a tumour-associated antigen.

In one embodiment, the liposomes or carbohydrate vehicles are targeted to HIV infected cells by putting viral antibodies on its surface. In another embodiment, the viral antibodies are directed to the HIV coat protein gp160 and/or gp120.

In another embodiment, the present invention is directed to a pharmaceutical formulation comprising a composition as described herein and a pharmaceutically acceptable carrier thereof.

In one embodiment the pharmaceutically acceptable carrier, which in one embodiment is a cyclodextrin, alpha-cyclodextrin, beta-cyclodextrin, (beta-hydroxypropylcyclodextrin) gamma-cyclodextrin and in another embodiment is vitamin E oil.

The compounds of the present invention can be formulated and administered as free bases or in the form of their pharmaceutically acceptable salts for purposes of stability, convenience of crystallisation, increased solubility, and the like.

The present invention is further directed to the use of a pharmaceutical formulation for the manufacture of a medicament for treatment of a mammal suffering from a neoplasia comprising a pharmaceutical formulation as described herein.

The present invention is also directed to the use of a pharmaceutical formulation for the manufacture of a medicament for sensitising a resistant neoplasia to subsequent therapy comprising administering to a patient in need thereof a therapeutically effective amount of composition as previously described.

The present invention is directed to a method of inhibiting neoplastic cells by exposing those cells to a pharmacologically effective amount of compositions

containing those compounds of the present invention described below, their derivatives, metabolites, analogues and/or mimic molecules with pharmaceutical acceptable additives, diluents, carriers and excipients. Such compounds are effective at eliminating and inhibiting the growth of neoplasias such as precancerous lesions, tumours and cancer growth. One of the advantages of utilising such compositions is that they are low in toxicity, which in combination with their mechanism of action diminishes resistance development.

The present invention provides compounds, their derivatives, metabolites, analogues and/or mimic molecules with pharmaceutical acceptable additives, diluents, carriers and excipients and pharmaceutically acceptable salts thereof, as well as pharmaceutical compositions comprising the compounds of the present invention, their derivatives, metabolites, analogues and/or mimic molecules with pharmaceutical acceptable additives, diluents, carriers and excipients and methods comprising inhibiting tumour growth or treating cancer by administering one or more of the compounds of the present invention, their derivatives, metabolites, analogues and/or mimic molecules with pharmaceutical acceptable additives, diluents, carriers and excipients.

The present invention also provides products that are useful for treating neoplasia with minimal toxic side effects unlike the high toxicity associated with standard chemotherapeutic agents.

The present invention is also directed to the use of a pharmaceutical formulation for the manufacture of a medicament for treatment of a mammal suffering from an immunodysregulatory condition comprising a composition as described herein to a subject.

The present invention is also directed to providing a composition that regulates immune responses.

These and other objects of the present invention will become apparent from the description of the Invention disclosed below, which descriptions are intended to limit

neither the spirit or scope of the invention but are only offered as illustrations of the preferred embodiments of the invention.

The present invention is directed to the treatment, inhibition and/or prevention of tumours and/or cancer growth and more particularly to treating neoplasia.

As used herein, the term "neoplasia" or neoplasm covers dysplasia, precancerous lesions, cancerous lesions, neoplastic cells, cancer, cancer growth, tumours, benign tumours, malignant tumours, solid tumours, carcinomas, etc.

As used herein, the term "precancerous lesion" includes syndromes represented by abnormal neoplastic, including dysplastic, changes of tissue. Examples include precancerous growths in colonic, breast, renal, central nervous, gastric, or lung tissues, or conditions such as dysplastic nevus syndrome, a precursor to malignant melanoma of the skin. Examples also include, in addition to dysplastic nevus syndromes, polyposis syndromes, colonic polyps, precancerous lesions of the cervix (i.e., cervical dysplasia), prostatic dysplasia, bronchial dysplasia, breast, bladder and/or skin and related conditions (e.g., actinic keratosis), whether the lesions are clinically identifiable or not.

The compounds of the present invention can be administered to a mammal having a susceptible cancer, i.e. a malignant cell population or tumour. Compounds of the present invention are effective on human tumours in vivo as well as on tumour cell lines in vitro. The compounds of the present invention may be particularly useful for the treatment of solid tumours for which relatively few treatments are available. Such tumours include epidermoid and myeloid tumours, acute or chronic, nonsmall cell, squamous. Specific cancers which may be mentioned as susceptible to treatment by administration of compounds in accordance with the present invention include prostate cancer, colon cancer, small cell lung cancer, large cell lung cancer, lung adenocarcinoma, epidermoid lung cancer, melanoma (including amelanotic subtypes), renal cell carcinoma, gastric carcinoma, cancers of the central nervous system (based on the likelihood that the compounds will cross the blood cell barrier) including brain tumours, neuroblastomas, gastric carcinoma, breast cancer, ovarian cancer, testicular cancer, lymphoma and leukaemia, oesophageal cancer, stomach cancer, liver cancers, prostate cancer, cervical cancer, adrenal cancer,

oral or mucosal cancer, bladder cancer, pancreatic cancer, lymphoma, Hodgkins disease, sarcomas. Hematopoeitic cell cancers such as B cell leukaemia/lymphomas, myelomas, T-cell leukemias/lymphomas, small cell leukemias/lymphomas, null cell, sezary, monocytic, myelomonocytic and Hairy cell leukemias. These lymphomas/leukemias can be either acute or chronic. Other cancers may also be susceptible to treatment with the compounds of the present invention. The activity can readily be measured using standardised tests known to those skilled in the art.

As used herein, the term "carcinomas" refers to lesions that are cancerous. Examples include malignant melanomas, breast cancer, and colon cancer. As used herein, the term "neoplasm" refers to both precancerous and cancerous lesions.

As used herein, the terms "inhibit" or "inhibiting," mean decreasing tumour cell growth rate from the rate that would occur without treatment and/or causing tumour mass to decrease. Inhibiting also includes causing a complete regression of the tumour. Thus the compounds of the present invention can be either cytostatic or cytotoxic to the tumour cells.

As used herein, the terms subject and patient are used interchangeably. Subjects and patients are mammals.

The compounds of the present invention are useful antineoplastic agents i.e. to inhibit tumour cell growth in vitro and in vivo, in mammalian hosts, such as humans or domestic animals, and are particularly effective against solid tumours and multidrug resistant tumours. Thus the invention provides a method comprising inhibiting cancer cells, by contacting said cells, in vitro and in vivo with an effective amount of at least one compound of the present invention. The invention also provides a therapeutic method comprising treating cancer (i.e. inhibiting tumour cell growth) by administering at least one of the compounds of the present invention to a mammal in need of such therapy.

The invention is directed to a method of treating tumours comprising administering a biologically active amount of a composition which consists of at least one compound of the present invention, their derivatives, metabolites, analogues and/or mimic molecules with pharmaceutical acceptable additives, diluents, carriers and excipients and pharmaceutically acceptable salts thereof.

The invention features a method of treating cancer comprising administering to a patient in need thereof a cancer treatment effective amount of a composition which consists of at least one compound of the present invention, their derivatives, metabolites, analogues and/or mimic molecules with pharmaceutical acceptable additives, diluents, carriers and excipients and pharmaceutically acceptable salts thereof.

It was surprisingly found that when a composition which consists of at least one compound of the present invention or their derivatives, metabolites, analogues or mimic molecules were administered, the proliferation of neoplastic cells was inhibited, which is manifested, pursuant to one aspect of the present invention, in a broad-spectrum anti-neoplastic activity.

The compounds of the present invention are individually diverse, but collectively all act to inhibit the propagation of neoplastic cells, cancers, cancer growth and/or tumours.

The invention also features a method of treating neoplasia comprising administering to a patient an effective amount of a composition which consists of at least one compound of the present invention and a pharmaceutically acceptable carrier.

Treating neoplasia in a patient includes achieving, partially or substantially, one or more of the following: arresting the growth or spread of a cancer, reducing the extent of a cancer (e.g., reducing size of a tumour or reducing the number of affected sites), inhibiting the growth rate of a cancer, and ameliorating or improving a clinical symptom or indicator associated with a cancer (such as tissue or serum components).

The present invention relates to specific compounds, defined herein, that display immuno-modulatory activity. It has been surprisingly found the compounds of the present invention have potent immuno-modulatory activity.

The present invention also relates to compositions and methods of treatment for prevention of an immunodysregulation condition.

The present invention also relates to specific compounds, defined herein, that enhance endogenous heat shock proteins (hsp) and precursor dendritic cell levels.

In accordance with the present invention, a method is provided to treat or prevent an immunodysregulatory condition comprising administering to a subject an effective amount of a composition which consists of at least one of the compounds of the present invention, their derivatives, metabolites, analogues and/or mimic molecules with pharmaceutical acceptable additives, diluents, carriers and excipients and pharmaceutically acceptable salts thereof.

The present invention also provides the use of compositions which consist of one or more of the compounds of the present invention, their derivatives, metabolites, analogues and/or mimic molecules with pharmaceutical acceptable additives, diluents, carriers and excipients and pharmaceutically acceptable salts thereof, for the manufacture of a medicament for an immunodysregulatory condition.

The present invention also provides compositions which consists of at least one compound of the present invention for use in a method of treatment of an immunodysregulatory condition, said method comprising administering one or more to a subject.

The pharmaceutical formulations may also be administered in combination with other therapeutic treatments, such as radiation treatment, surgery or in combination with other anticancer, antiviral or antiparasite drugs. The formulations of the present invention may further include as optional ingredients one or more chemotherapeutic agents already known for their use in the inhibition of cancer cells, for added clinical

efficacy. Such combinations will in some cases provide added benefit.

In one embodiment, the pharmaceutical formulation further includes at least one conventional chemotherapeutic agent.

In another embodiment, the conventional chemotherapeutic agent is selected from the group comprising flutamide and luprolide, antioestrogens, such as tamoxifen, antimetabolites and cytotoxic agents, such as daunorubicin, flourouracil, floxuridine, interferon alpha, methotrexate, plicamycin, mecaptopurine, thioguanine, adramycin, carmustine, lomustine, cytarabine, cyclophosphamide, doxorubicin, estramustine, altretamine, hydroxyurea, ifosfamide, procarbazine, mutamycin, busulfan, mitoxantrone, carboplatin, cisplatin, streptozocin, bleomycin, dactinomycin and idamycin, hormones such as, medroxyprogesterone, estramustine, ethinyl oestradiol, oestradiol, leuprolide, megestrol, octreotide, diethylstilbestrol, chlorotrianisene, etoposide, podophyllotoxin, and goserelin, nitrogen mustard derivatives such as, melphalan, chlorambucil, methlorethamine and thiotepa, steroids such as, betamethasone, and other antineoplastic agents such as live *Mycobacterium bovis*, dicarbazine, asparaginase, leucovoribn, mitotane, vincristine, vinblastine and texotere, cyclophosphamide, adriamycin, 5-flourouracil, hexamethylmelamine, Acivicin; Aclarubicin; Acodazole Hydrochloride; AcrQnine; Adozelesin; Aldesleukin; Altretamine; Ambomycin; Ametantrone Acetate; Aminoglutethimide; Amsacrine; Anastrozole; Anthramycin; Asparaginase; Asperlin; Azacitidine; Azetepa; Azotomycin; Batimastat; Benzodepa; Bicalutamide; Bisantrene Hydrochloride; Bisnafide Dimesylate; Bizelesin; Bleomycin Sulfate; Brequinar Sodium; Bropirimine; Busulfan; Cactinomycin; Calusterone; Caracemide; Carbetimer; Carboplatin; Carmustine; Carubicin Hydrochloride; Carzelesin; Cedefingol; Chlorambucil; Cirolemycin; Cisplatin; Cladribine; Crisnatol Mesylate; Cyclophosphamide; Cytarabine; Dacarbazine; Dactinomycin; Daunorubicin Hydrochloride; Decitabine; Dexormaplatin; Dezaguanine; Dezaguanine Mesylate; Diaziquone; Docetaxel; Doxorubicin; Doxorubicin Hydrochloride; Droloxifene; Droloxifene Citrate; Dromostanolone Propionate; Duazomycin; Edatrexate; Eflomithine Hydrochloride; Elsamitrucin; Enloplatin; Enpromate; Epipropidine; Epirubicin Hydrochloride; Erbulozole; Esorubicin Hydrochloride; Estramustine;

Estramustine Phosphate Sodium; Etanidazole; Ethiodized Oil I 131; Etoposide; Etoposide Phosphate; Etoprine; Fadrozole Hydrochloride; Fazarabine; Fenretinide; Floxuridine; Fludarabine Phosphate; Fluorouracil; Flurocitabine; Fosquidone; Fostriecin Sodium; Gemcitabine; Gemcitabine Hydrochloride; Gold Au 198; Hydroxyurea; Idarubicin Hydrochloride; Ifosfamide; Ilmofosine; Interferon Alfa-2a; Interferon Alfa-2b; Interferon Alfa-n1; Interferon Alfa-n3; Interferon Beta- I a; Interferon Gamma- I b; Iproplatin; Irinotecan Hydrochloride; Lanreotide Acetate; Letrozole; Leuprolide Acetate; Liarozole Hydrochloride; Lometrexol Sodium; Lomustine; Losoxantrone Hydrochloride; Masoprocol; Maytansine; Mechlorethamine Hydrochloride; Megestrol Acetate; Melengestrol Acetate; Melphalan; Menogaril; Mercaptopurine; Methotrexate; Methotrexate Sodium; Metoprine; Meturedepa; Mitindomide; Mitocarcin; Mitocromin; Mitogillin; Mitomalcin; Mitomycin; Mitosper; Mitotane; Mitoxantrone Hydrochloride; Mycophenolic Acid; Nocodazole; Nogalamycin; Ormaplatin; Oxisuran; Paclitaxel; Pegaspargase; Peliomycin; Pentamustine; Peplomycin Sulfate; Perfosfamide; Pipobroman; Piposulfan; Piroxantrone Hydrochloride; Plicamycin; Plomestane; Porfimer Sodium; Porfiromycin; Prednimustine; Procarbazine Hydrochloride; Puromycin; Puromycin Hydrochloride; Pyrazofurin; Riboprine; Rogletimide; Safmgol; Safingol Hydrochloride; Semustine; Simtrazene; Sparfosate Sodium; Sparsomycin; Spirogermanium Hydrochloride; Spiromustine; Spiroplatin; Streptonigrin; Streptozocin; Strontium Chloride Sr 89; Sulofenur; Talisomycin; Taxane; Taxoid; Tecogalan Sodium; Tegafur; Teloxantrone Hydrochloride; Temoporfin; Teniposide; Teroxirone; Testolactone; Thiamiprine; Thioguanine; Thiotepa; Tiazofurin; Tirapazamine; Topotecan Hydrochloride; Toremifene Citrate; Trestolone Acetate; Triciribine Phosphate; Trimetrexate; Trimetrexate Glucuronate; Triptorelin; Tubulozole Hydrochloride; Uracil Mustard; Uredepa; Vapreotide; Verteporfin; Vinblastine Sulfate; Vincristine Sulfate; Vindesine; Vindesine Sulfate; Vinepidine Sulfate; Vinglycinate Sulfate; Vinleurosine Sulfate; Vinorelbine Tartrate; Vinrosidine Sulfate; Vinzolidine Sulfate; Vorozole; Zeniplatin; Zinostatin; Zorubicin Hydrochloride, 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; atrsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors;

antagonist D; antagonist G; DHEA; bromineepiandrosterone; epiandrosterone; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocannycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflomithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; fmasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-;

irinotecan; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A +myobacterium cell wall sk; mopidamol; multiple drug resistance genie inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone +pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed;

ramosetron; ras famesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfmosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thalidomide; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene dichloride; topotecan; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; venom, anti-venom, veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, Immunostimulating drugs or therapeutic agents, their metabolites, salts and derivatives thereof .

In one embodiment, the composition further includes at least one anti-viral agent.

In one embodiment, the anti-viral agents are selected from the group comprising nucleoside analogues (AZT; ddC; ddI; d4T; 3TC; BW 1592; PMEA/bis-POM PMEA; dOTC; DAPD); non-nucleoside reverse transcriptase inhibitors (delavirdine; DMP 266; HBY097; loviride; nevirapine, emivirine; AG1549; PNU142721; Calanolide A; DPC961); protease Inhibitors (ABT-378; ritonavir; nelfinavir; BW 141; KNI-272;

indinavir; saquinavir; L-756,423; DMP-450; BMS-232630); ALX40-4C; hydroxyurea; lobucavir; pentafuside; T-1249; PRO 542; FP-21399; AMD 3100; HE-2000 and peptide T; Abacavir; Acemannan; Acyclovir; Acyclovir Sodium; Adefovir; Alovudine; Alvircept Sudotox; Amantadine Hydrochloride; Aranotin; Arildone; Atevirdine Mesylate; Avridine; Cidofovir; Cipamfylline; Coviracil; Cytarabine Hydrochloride; Delavirdine Mesylate; Desciclovir; Didanosine; Disoxaril; Edoxudine; Emivirine; Emtricitabine; Enviradene; Enviroxime; Epivir; Famciclovir; Famotine Hydrochloride; Fiacitabine; Fialuridine; Fosarilate; Foscarnet Sodium; Fosfonet Sodium; Ganciclovir; Ganciclovir Sodium; Idoxuridine; Indinavir; Kethoxal; Lamivudine; Lobucavir; Lodenosine; Lopinavir, Memotine Hydrochloride; Methisazone; Nelfinavir; Nevirapine; Penciclovir; Pirodavir; Ribavirin; Rimantadine Hydrochloride; Saquinavir Mesylate; Ritonavir; Somantadine Hydrochloride; Sorivudine; Statolon; Stavudine; Tenofovir; Tilorone Hydrochloride; Trifluridine; Valacyclovir Hydrochloride; Vidarabine; Vidarabine Phosphate; Vidarabine Sodium Phosphate; Tipranavir, Viroxime; Zalcitabine; Zidovudine; Zinviroxime and Interferon.

In one embodiment, the composition further includes at least one anti-parasite agent.

In one embodiment, the anti-parasite agents are selected from the group comprising chloroquin, primaquine, mefloquine, pyrimethamine-sulfadoxone, atoraquone/dapsone; halofantrine; artemisinin derivatives; atoraquone + proguanol, co-artemether; podophyllotoxin; pentamidine, diloxanide furoate, metronidazole, tindazole, tetracycline, quinacrine, stibogluconate, amphotericin B, quinine, doxycline, trimethoprim-sulfamethoxazole, metronidazole, nifurtimox, suramin, melarsoprol, benznidazole, their metabolites, salts derivatives or any other anti-parasitic agent thereof .

The agents of the present invention may also be administered in combination with other agents for example immunostimulating drugs or therapeutic agents. Appropriate amounts in each case will vary with the particular agent, and will be either readily known to those skilled in the art or readily determinable by routine

experimentation.

In one embodiment, the pharmaceutical formulation is administered in combination with radiation treatment.

In one embodiment, the pharmaceutical formulation is administered in combination with surgery.

The invention also relates to a method of suppressing tumour growth in a mammal by administering to the mammal an amount of a composition which consists of at least one of the compounds of the present invention, derivatives, metabolites, analogues and/or mimic molecules, and a second chemotherapeutic agent effective to suppress tumour growth in the mammal. The second chemotherapeutic agent is not a compound of the present invention or a derivative, metabolite, analogue or mimic molecule. These compositions provide enhanced antitumour effect and may also prevent the development of metastases. In particular, these compounds are useful for overcoming tumours that are drug resistant. These agents may be administered separately or as a cocktail. Toxicity may be reduced by administering the compound of the present invention or a derivative, metabolite, analogue or mimic molecule, thereof several hours prior to administering the chemotherapeutic agent. The compositions can be administered by any route.

The components of any of the pharmaceutical formulations disclosed herein can be administered simultaneously (in a combination formulation), essentially simultaneously (e.g., administration of each compound a few minutes or a few hours apart), or can be administered sequentially, e.g., several days apart, or more than a week apart. For example, a compound of the present invention, (and a conventional chemotherapeutic agent) can be administered together, or essentially simultaneously, e.g., administration of each compound a few minutes or a few hours apart, or can be administered sequentially, e.g., several days apart, or more than a week apart. All such variations in administration of the combination therapy are encompassed within the scope of the invention.

In one embodiment, the neoplasia is a precancerous lesion including syndromes represented by abnormal neoplastic and/or dysplastic, changes of tissue comprising precancerous growths in colonic, breast, renal, central nervous, gastric, or lung tissues, or conditions such as dysplastic nevus syndrome, a precursor to malignant melanoma of the skin, dysplastic nevus syndromes, polyposis syndromes, colonic polyps, precancerous lesions of the cervix (i.e., cervical dysplasia), prostatic dysplasia, bronchial dysplasia, breast, bladder and/or skin and related conditions (e.g., actinic keratosis), whether the lesions are clinically identifiable or not.

In one embodiment, the neoplasia is prostate cancer, colon cancer, small cell lung cancer, large cell lung cancer, lung adenocarcinoma, epidermoid lung cancer, melanoma (including amelanotic subtypes), renal cell carcinoma, gastric carcinoma, cancers of the central nervous system including brain tumours, neuroblastomas, gastric carcinoma, breast cancer, ovarian cancer, testicular cancer, lymphoma and leukaemia, oesophageal cancer, stomach cancer, liver cancers, prostate cancer, cervical cancer, adrenal cancer, oral or mucosal cancer, bladder cancer, pancreatic cancer, lymphoma, Hodgkins disease, sarcomas. Hematopoeitic cell cancers such as B cell leukaemia/lymphomas, myelomas, T-cell leukemias/lymphomas, small cell leukemias/lymphomas, null cell, sezary, monocytic, myelomonocytic and Hairy cell leukemias.

In one embodiment, the neoplasia is in the form of a tumour comprising an epidermoid and myeloid tumour, acute or chronic, nonsmall cell, squamous or solid.

It has been surprisingly found that the compounds of the present invention have potent immuno modulatory effects. Accordingly, the disclosed compounds of the present invention when administered to human patients will have a broad immuno-modulatory effect, resulting in its application in many syndromes, especially following treatment for or infection by cancerous cells. More specifically, one aspect of the present invention relates to the use of the compounds of the present invention In treatment of an immunodysregulation condition.

According to one aspect of the invention, a composition containing at least one of the compounds of the present invention enhance the production of endogenous heat shock protein (hsp) production, regardless of the immunocompetency of the individual. According to another aspect of the invention, a composition containing at least one of the compounds of the present invention enhance levels of precursor dendritic cells.

The advantage of administering a pharmaceutical formulation containing at least one compound of the present invention with a suitable carrier is three fold:

1. The cancer-infected cell is presented to the immune system where its presence is detected due to enhanced immunosurveillence.
2. The compounds of the present invention have immuno up-regulatory properties, precursor dendritic and natural killer cells are up regulated. Antigen capture is further enhanced by a domino effect of increasing precursor dendritic cell maturation into cytotoxic T cells.
3. The presentation of the antigenic peptides to the cytotoxic T cells is improved.

In one embodiment, a pharmaceutical formulation is provided to enhance endogenous hsp levels, comprising administering to a patient in need thereof a therapeutically effective amount of a composition comprising at least one compound of the present invention.

In another embodiment, a method for enhancing endogenous hsp levels in a living subject is provided, comprising administering to a patient in need thereof a therapeutically effective amount of a composition comprising at least one compound of the present invention.

In another embodiment, a method of treating the symptoms of low levels of endogenous hsp levels in a living subject is provided, comprising administering to a patient in need thereof a therapeutically effective amount of a composition comprising at least one compound of the present invention.

In another embodiment, a pharmaceutical formulation is provided to enhance endogenous precursor dentritic cell levels, comprising administering to a patient in need thereof a therapeutically effective amount of a composition comprising at least one compound of the present invention.

Additionally, the invention provides use of the composition to provide protection against infections in immunocompromised animals and humans. These compositions may be used prophylactically or therapeutically to protect animals or patients from the consequences of infection by pathogens.

Further, the invention provides use of the composition in veterinary medicine, prophylactically and therapeutically in animal populations that are subject to infection that compromises immune response and cause infection.

In another aspect of the invention, the use of a pharmaceutical formulation is provided for the manufacture of a medicament for the treatment of a mammal suffering from an immuno dysregulation condition, comprising administering to a patient in need thereof a therapeutically effective amount of a a pharmaceutical formulation of the present invention.

In one embodiment, the immuno dysregulation condition is caused by a viral infection, intracellular bacterial infection, extracellular bacterial infection, fungal infection, yeast infection, extracellular parasite infection, intracellular parasite infection, protozoan parasite, multicellular parasite, autoimmune disease, immunosuppressive therapy, chemotherapy, anti-infective agent therapy, wound, burn, the presence of an immunosuppressive molecule, gastrointestinal Irritation or any combination of the foregoing and is selected from (a) a DNA virus infection or an RNA virus(b) a parasite infection, a *Trypanosoma*, *Plasmodium*, *Cryptosporidium*, *Entamoeba*, *Balantidium*, *Leishmania*, *Pneumocystis*, *Trichomoniasis* or *Toxoplasma* infection, wherein the *Trypanosoma*, *Plasmodium*, *Cryptosporidium*, *Entamoeba*, *Balantidium*, *Leishmania*, *Pneumocystis*, *Trichomoniasis* or *Toxoplasma* infection Is selected from but not limited to *Trypanosoma cruzi*, *Trypanosoma brucei*, *Trypanosoma gambiense*, *Trypanosoma*

rhodesiense, Plasmodium falciparum, Plasmodium vivax, Plasmodium malariae, Plasmodium ovale, Plasmodium berghei, Entamoeba histolytica, Balantidium coli, Leishmania brazilienis, Leishmania mexicana, Leishmania donovani, Leishmania tropica, Pneumocystis carinii, Trichomoniasis vaginalis, and *Toxoplasma gondii* (c) a mycoplasma infection, a *Listeria* infection or a *Mycobacterium* infection; (d) *a Streptococcus* infection, *a Staphylococcus* infection, a *Vibrio* infection, a *Salmonella* infection; *a Shigella* infection, an enterotoxigenic, enteropathogenic, enteroinvasive or enterohemorrhagic *E. coli* infection, a *Yersinia* infection, a *Campylobacter* infection, *a Pseudomonas* infection, *a Borrelia* infection, a *Legionella* infection and *a Haemophilus* infection; (e) pulmonary *Aspergillosis*, mucosal or oropharyngealcandidiasis and juvenile paracoccidiomyosis; (f) *a Candida* infection and *a Cryptococcus* infection; (g) systemic lupus erythematosis, arthritis, asthma, and diabetes (h) adriamycin treatment, cisplatin treatment, mitomycin C treatment, amphoteracin B treatment; (i) a gamma-radiation treatment; (j) nucleoside analog treatment for viral infection or for cancer; (k) surgical and accidental wounds, septic shock caused by surgery; (l) cyclosporin treatment and corticosteroid treatment; (m) irritable bowel treatment, Crohn's disease, wasting syndrome, cachexia, Motor Neuron disease, Multiple Sclerosis, inflammatory bowel disease, respiratory distress syndrome, chronic diarrhoea; (n) cancer; (o) cirrhoisis; (p) gram positive multi-drug resistant bacteria or (q) any combination of (a) through (p).

In one embodiment, the DNA virus infection or the RNA virus infection is selected from *a* retrovirus infection, a togavirus infection, *a* flavivirus infection, a rubivirus infection, a pestivirus infection, a lipid envelope virus infection, *a* filovirus, a picornavirus infection, a rhinovirus infection, *a* coronavirus infection, a respiratory syncytial virus infection, *a* poliovirus infection, *a* parainfluenza virus infection, influenza virus infection, hantavirus, adeno-associated virus, measles virus, poxvirus, filovirus, human papilloma virus and animal papilloma virus infection.

In one embodiment, the composition enhances endogenous hsp levels.

In one embodiment, the composition enhances endogenous precursor dendritic cell

levels.

The invention also relates to a method for reducing the immunodepressive effect of a chemotherapy agent in a mammal by administering to a mammal an amount of a composition which consists of at least one compound of the present invention or a derivative, metabolite, analogue or mimic molecule thereof effective to augment the immune system of the mammal upon treatment of the mammal with the chemotherapeutic agent. The immune system may be augmented, for example, by increasing the total number of leukocytes, T-lymphocytes, B-lymphocytes, or immunoglobulins.

The present invention also provides a method of sentisizing a neoplasia to subsequent treatment, for example radiation or chemotherapy. It is known that cancer cells become resistant to some chemotherapeutic agents and are even resistant to many different chemotherapeutic agents. This is a significant to many different chemotherapeutic treatments. This method includes administering an effective amount of a composition which consists of at least one compound of the present invention or a derivative, metabolite, analogue or mimic molecule thereof to a mammal having cancer.

In another aspect of the invention, the use of a pharmaceutical formulation is provided for the manufacture of a medicament for sensitising a resistant neoplasia to subsequent therapy comprising administering to a patient in need thereof a therapeutically effective amount of a a pharmaceutical formulation of the present invention.

The method of the present invention is useful in sensitizing desensitized cancer cells in particular: ovarian, sarcoma, non-Hodgkin's lymphoma, lung, breast cancer, bladder carcinoma, colon carcinoma, pancreatic carcinoma, carcinoma of the ampulla of Vater, multiple myeloma, adult acute lymphocytic leukemia, adult non-lymphoytic leukemia and neuroblastoma. It is preferred that the cancer cells be breast cancer, multiple myeloma, ovarian or lung.

It is realized that the desensitized cancer cells may be desensitized to more than one chemotherapeutic agent. If so, the method of the present invention will

sensitize the desensitized cancer cells to most of the chemotherapeutic agents to which they are desensitized.

In one embodiment, the chemotherapeutic agents to which the cancer cells become desensitized are selected from the group consisting of doxorubicin, daunomycin, vinca alkaloids, vincristine, vinblastine, taxol, colchicine, epipodophyllotoxins such as etoposide, actinomycin D, puromycin, emetine, melphalan, adozelesin, [S-(R,R)] 6,6'-[carbonylbis(imino-1H-indole-05,2-diylcarbonyl)]bis[8-(chloromethyl) 3,6,7,8-tetrahydro-1-,methyl-benzo[l ,2-b;4,3-b']dipyrrol-4-l, (S)-N-[2-[[1-(chloromethyl)-1,6-dihydro-8-methyl-5-[[(phenylamino)carbonyl]opxy]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1H-indol-5-yl]-6-(diethylamino)-2 benzofurancarboxamide, (7bR, 8aS)-7-[[1 ,6-dihydro-4-hydroxy-5-methoxy-7-[(4,5, 8, 8a-tetrahydro-7-methyl-4- oxocyclopropa[c]pyrrolo [3 ,2-e] indol-2(1H)-yl)carbonyl]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-4-hydroxy-5-methoxybenzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide.

It is realized that new chemotherapeutic agents against cancer will be developed after this invention. The new chemotherapeutic agents to which resistance develops and which can be treated by the method of this invention are equivalent to those set forth in this invention.

In one embodiment, the pharmaceutical formulation has an enteric coating. In one embodiment, the enteric coating is made of a polymer or copolymer. In one embodiment, the polymer or copolymer is selected from the group consisting of poly(lactic-glycolic acid) polyester, cellulose acetate phthalate, hydroxypropyl-methyl cellulose phthalate poly(butyl methacrylate), (2-dimethyl aminoethyl) methacrylate, and methyl methacrylate.

The pharmaceutical formulation according to the present invention can be administered to a patient in any of a wide range of routes. Thus, with regard to the types of formulations in which the active compounds according to the present invention can be administered, as well as any additives can be included with the

active compounds in the formulations, and the possible routes of administration, it is well known to those of skill in the art that such formulations can be provided in a wide variety of types, and it is within the skill of the ordinary artisans to select a specific formulation and route of administration and then test suitability for use. By way of example but not limitation, suitable routes include enteric, parenteral, topical, oral, rectal, nasal or vaginal routes. Parenteral routes include subcutaneous, intramuscular, intravenous, intraperitoneal, intradermal and sublingual administration. Also, compositions may be implanted into a patient or injected using a drug delivery system.

The pharmaceutical formulation according to the present invention may be administered locally or systemically. By systemic administration means any mode or route of administration that results in effective amounts of active ingredient appearing in the blood or at a site remote from the route of administration of the active ingredient.

Further, the pharmaceutical formulation according to the present invention may be administered intermittently. The advantage of this is that it allows the patient to suspend therapy for periods without the worry of inactivity of the drug resulting from the development of resistant cells.

The pharmaceutical formulation according to the invention may be formulated for enteral, parenteral or topical administration. Indeed all three types of formulations may be used simultaneously to achieve systemic administration of the active ingredient.

Compounds useful in the methods of this invention may be formulated into compositions together with pharmaceutically acceptable carriers for oral administration in solid or liquid form, or for rectal administration, although carriers for oral administration are most preferred.

Pharmaceutically acceptable carriers for oral administration include capsules, tablets, pills, powders, troches and granules. In such solid dosage forms, the

carrier can comprise at least one inert diluent such as sucrose, lactose or starch. Such carriers can also comprise, as is normal practice, additional substances other than diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, troches and pills, the carriers may also comprise buffering agents. Carriers such as tablets, pills and granules can be prepared with enteric coatings on the surfaces of the tablets, pills or granules. Alternatively, the enterically coated compound can be pressed into a tablet, pill, or granule, and the tablet, pill or granules for administration to the patient. Preferred enteric coatings include those that dissolve or disintegrate at colonic pH such as shellac or Eudraget S. Additional pharmaceutically acceptable carriers include liquid dosage forms for oral administration, e.g. pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs containing inert diluents commonly used in the art, such as water. Besides such inert diluents, compositions can also include adjuvants such as wetting agents, emulsifying and suspending agents, and sweetening, flavouring and perfuming agents.

Pharmaceutically acceptable carriers for rectal administration are preferably suppositories that may contain, in addition to the compounds of the present invention, excipients such as cocoa butter or a suppository wax.

Suitable injectable solutions include intravenous, subcutaneous and intramuscular injectable solutions. Examples of injectable forms include solutions, suspensions and emulsions. Typically the compound(s) is injected in association with a pharmaceutical carrier such as normal saline, Ringers solution, dextrose solution and other aqueous carriers known in the art. Appropriate non-aqueous carriers may also be used and examples include cyclodextrin, preferably hydroxypropyl beta cyclodextrin, mixed oils (vitamin E oil), polyethylene glycol and ethyl oleate. A preferred carrier is cyclodextrin in water. Frequently, it is desirable to include additives in the carrier such as buffers and preservatives or other substances to enhance isotonicity and chemical stability.

The composition can also be administered topically. Suitable formulations for topical administration include creams, gels, jellies, mucliages, pastes and ointments. The

compounds may be formulated for transdermal administration, for example in the form of transdermal patches so as to achieve systemic administration.

The composition may also be administered in the form of an implant.

The composition may also be administered in the form of an infusion solution or as a nasal inhalation, aerosol or spray.

In another embodiment, the composition is incorporated in a pharmaceutically acceptable carrier, diluents, vehicles and the like for systemic administration by feeding. An example of such a carrier is cyclodextrin (α-cyclodextrin, β-hydroxypropylcyclodextrin or γ-cyclodextrin).

In one embodiment, the pharmaceutical formulation is administered enterally, parenterally, topically, orally, sub-lingually, rectally, nasally or vaginally.

In one embodiment, the pharmaceutical formulation is administered to a mammal. In one embodiment, said mammal is a neonate and said administering is effected prior to delivery of said neonate and/or during delivery of said neonate.

The pharmaceutically acceptable carrier and compounds of this invention are formulated into unit dosage forms for administration to a patient. The dosage levels of active ingredient (i.e. compounds of this invention) in the unit dosage may be varied so as to obtain an amount of active ingredient effective to achieve lesion-eliminating activity in accordance with the desired method of administration (i.e., oral or rectal). The selected dosage level therefore depends upon the nature of the active compound administered, the route of administration, the desired duration of treatment, individual needs and other factors. If desired, the unit dosage may be such that the daily requirement for active compound is in one dose, or divided among multiple doses for administration, e.g., two to four times per day.

With regard to dosage and duration of treatment according to any aspect of the present Invention, it is recognized that the ability of an artisan skilled in

pharmaceutical administration of drugs to determine suitable dosages depending on many inter-related factors is well known, and skilled artisans are readily able to monitor patients to determine whether treatment should be started, continued, discontinued or resumed at any given time. For example, dosages of the compounds are suitably determined depending on the individual cases taking symptoms, age and sex of the subject and the like into consideration. The amount of the compound to be incorporated into the pharmaceutical composition of the invention varies with dosage route, solubility of the compound, administration route, administration scheme and the like. An effective amount for a particular patient may vary depending on factors such as the condition being treated, the overall health of the patient and the method, route and dose of administration. The clinician using parameters known in the art makes determination of the appropriate dose. Generally, the dose begins with an amount somewhat less than the optimum dose and it is increased by small increments thereafter until the desired or optimum effect is achieved. Suitable dosages can be determined by further taking into account relevant disclosure in the known art. In one embodiment, the unit dose comprises 5-500 mg of active ingredient consisting of at least one compound of the present invention.

The pharmaceutical formulations of this invention are preferably packaged in a container (e.g. a box or bottle, or both) with suitable printed material (e.g. a package insert) containing indications, directions for use, etc.

The present invention is also directed to compositions which consist of at least one compound if the present invention acting as prodrug compounds analogous to the active compounds disclosed herein. Such compounds are generally themselves inactive or low in activity, but are converted into active compounds. Thus, for example, pro-drugs such as the methyl ester of any acid functionality, which is not active *per se* or has very low activity could be hydrolysed, either uncatalytically or catalytically with an enzyme such as an esterase, to an active compound. Such pro-drug compounds could well be the preferred therapeutic form of the present compounds. These analogous prodrugs can be produced from active compounds

based on procedures and factors that are well known to one of ordinary skill in the art. Accordingly as used in the present application, "pro-drug analogue" means "a chemical which is relatively non-toxic and pharmacologically inert but which can be transformed *in vivo* to a pharmacologically active drug". More specifically it means a derivative, metabolite or analogue of the compounds of the present invention which have low or no ability as anti-neoplastic agents until converted in the body to a derivative, metabolite or analogue with such ability or abilities. Such pro-drugs should have favourable properties such as enhanced absorption, water solubility, lower toxicity, or better targeting to the tumour cell (such as by reason of greater affinity to the tumour cell or a larger quantity of activating enzyme in the tumour cell as opposed to a normal cell so that larger concentrations of the active compound are produced in the tumour cell). Examples of such compounds are esters, such as methyl, ethyl, phenyl, N,N-dimethylaminoethyl, acyl derivatives such as benzoyl, p-N,N-dimethylaminobenzoyl, N,N-dimethylaminoglycyl, peptide derivatives such as γ-glutamyl, glycyl, D-Val-Leu-Lys.

In one embodiment, said compounds of the present invention acts as a prodrug.

The compositions containing the active compounds or pro-drugs of the present invention can be formulated so as to be specifically targeted to tumours. The compounds can be attached to the reagent that is capable of binding a tumour-associated antigen. For example, the compounds of the present invention could be covalently attached to a monoclonal antibody such as directed to a tumour-associated antigen. The antigen may be located on a tumour or in the tumour cell area. Such linkages can be made through peptide bond formation with amino groups of an antibody. Suitable reagents include polyclonal and monoclonal antibodies. Accordingly, the present invention also provides a method comprising treating cancer (i.e. inhibiting tumour cell growth) by administering a pharmaceutical composition comprising at least one of the compounds of the present invention and a reagent (i.e. monoclonal or polyclonal antibody) which is capable of binding to a tumour associated antigen.

Alternatively, the compounds of the present invention could be attached to or incorporated into liposomes or carbohydrate vehicles, which are known to be useful for targeting anti-cancer drugs. Preferably the liposomes or carbohydrate vehicles can be specifically targeted to tumours by covalently attaching a monoclonal antibody directed to a tumour-associated antigen.

The invention further provides a composition for treating a cancer selected from the group consisting of small cell lung cancer, testicular cancer, lymphoma, leukaemia, oesophageal cancer, stomach cancer, colon cancer, breast cancer, central nervous system cancer, liver cancer and prostate cancer, which comprising administering to a mammal in need thereof an effective amount of a composition containing as an active ingredient therein at least one of the compounds of the present invention, their derivatives, metabolites, analogues and/or mimic molecules with pharmaceutical acceptable additives, diluents, carriers, excipients and pharmaceutical salts thereof.

The invention provides a method for inducing cellular differentiation, which comprises contacting a cancerous cell with an effective amount of at least one compound of the present invention or a derivative, metabolite, analogue or mimic molecule and pharmaceutically acceptable salts thereof.

The invention provides pharmaceutical formulations which consist of compositions comprising, at least one compound of the present invention and corresponding pharmaceutically acceptable derivatives, metabolites, analogues, mimic molecules and mixtures thereof are to be used as anti-neoplasic and/or anti-cancer agents.

The invention provides pharmaceutical formulations to be used in the preparation of medicaments having anti-neoplastic and/or anti-cancer activity.

The invention further provides, the use of the pharmaceutical formulations as anti-neoplasic and/or anti-cancer agents.

In another embodiment, the use of pharmaceutical formulations for the preparation of medicaments having anti-neoplastic and/or anti-cancer activity.

In another embodiment, pharmaceutical formulations are provided, for the preparation of medicaments having activity against neoplasm and/or cancer.

The present invention is exemplified in terms of in vitro and in vivo activity against various neoplastic cell lines. The test cell lines employed in the in vitro assays are well recognised and accepted as models for anti-tumour activity in animals. The term animals as used herein includes, but is not limited to, mice, rats, domesticated animals such as but is not limited to, cats, dogs, and other animals but Is not limited to, cattle, sheep, pigs, horses, and primates such as but not limited to, monkeys, humans and more generally mammals.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, practice the present invention to its fullest extent. The following detailed examples describe how to test the various compounds of this invention and/or perform the various processes of the invention and are to be construed as merely illustrative, and not limitations of the preceding disclosure in any way whatsoever. Those skilled in the art will promptly recognize appropriate variations from the procedures.

The active components with anti-neoplastic activity were extracted from resins of plants from the plant family *Burseraceae*, primarily Myrrh (*Commiphora* spp.) and Frankincense or Olibanum (*Boswellia carteri*). The components were extracted from the resins using standard extraction techniques followed by chromatographic isolation. Sample components were identified using several methods including preparative HPLC, mass spectroscopy, NMR spectroscopy, and IR and UV spectroscopy.

Multiple components can be extracted from the resins including: incensole, incensole acetate, incensole oxide, incensole oxide acetate, isoincensole, isoincensole acetate, isoincensole oxide, octyl acetate, octanol, terpinyl acetate, bornyl acetate, trans-ver-

benol, verbenone, menthadien-7-ol, terpinen-4-ol, trans-pinocarveol, carvone, borneol, famesol, farnesene, β-caryophyllene, humulene, β-cadinene, bergamotone, β-guaiene, β-ylangene, β-bourbonene, α-copaene, terpinene, myrcene, ρ-cymene, α- and β-phellandrene, α-thujene, cembranes, cembrane-A, isocembrane, cembranol, cembranoids, cembranoid alcohols, furanogermacrens, furanogermacrene, germacrene, elemane, cadinene, guaiane, oplopane, eudsmane, echinodol, α-santalene, α-bisabolene, furanodiene, β-santalene, β-bergamotene, β-famesene, β-bisabolene, T-cadinol, SKB4.

It is thought that multiple components could contribute to the anti-neoplasic components of the extracts. However the most active anti-neoplasic components comprised the diterpenoids incensole, incensole acetate, incensole oxide, incensole oxide acetate, isoincensole, isoincensole acetate, isoincensole oxide, and the furanosesquiterpene furnogermacrens in highest concentrations.

Example 1

In vitro cytotoxic activity of extracts containing high concentrations of incensole, furanogermacren and incensole/furanogermacren mixture were determined in several cultured tumour cell lines by performing the MTT clonogenic assay. This assay assesses the inhibition of colony formation of tumour stem cells growing in soft agar by cytotoxic agents. Since tumour stem cells are responsible for the proliferate potential and aggressiveness of a tumour cell population, the clonogenic assay is highly predictive of in vivo response.

Drugs and chemicals

The extracts were dissolved in DMSO/water 1:1, prepared as a 30 mg/ml solution and stored at –20°C until use. Final dilutions of all drugs were prepared in culture medium immediately prior to use. 5-Flourouracil was used as a positive control and purchased from Lederle (Hamburg).

CLONOGENIC ASSAY

Single cell suspension from tumour cell lines

Human tumour cell lines were grown in RPMI 1640 supplemented with 10% fetal

calf serum and 2 mM L-glutamine. The cells were kept at 5% CO_2 and 37°C and passaged routinely. For treatment experiments, exponentially growing cells were trypsinized, washed twice with PBS and the percentage of viable cells was determined by hemocytometer count using trypan blue viable dye exclusion.

Culture methods

The clonogenic assay was performed according to a modified two-layered soft agar assay. The bottom layer consisted of 0.2 mls of Iscove's Modified Dulbecco's Medium with 20% fetal calf serum and 0.75% agar. 2.5 X 104 cells in RPMI/10% FCS were added in 0.2 ml medium, but containing 0.4% agar and placed in 24-multiwell plates on top of the base layer. After 24 hours, drugs were added in additional 0.2 ml of RPMI medium. Every plate contained 6 vehicle controls and 6 different drug concentrations in triplicate. 5-flourouracil was used as a positive control in concentrations of 100, 300 and 1000 µg/ml. Cultures were incubated at 5% CO_2 and 37°C in a humidified atmosphere for 5 – 6 days under continuous exposure to drugs and monitored closely for colony growth using an inverted microscope. Within this period, *in vitro* tumour growth led to the formation of colonies with a diameter of 50 µm. At the time of colony formation, counts were performed with automated image analysis system (OMNICOM FAS IV, Biosys GmbH). Vital colonies were stained with a sterile aqueous solution of 2-(4-iodophenyl)-3-(4-nitrophenyl)-5-phenyltetrazolium chloride (1 mg/ml, 100 µl/well) 24 hours prior to evaluation. Drug effect was assessed in terms of percentage of survival obtained by comparison to the mean number of colonies in the treated wells with mean colony count of the untreated controls: treated controls X 100 (%T/C).

A compound was considered active if it reduces the colony formation to 30% or less of the control group value (T/C 30%). IC_{50} and IC_{70} values, representing the drug concentration to inhibit colony formation by 50% (T/C 50%) and 70% (T/C 30%) respectively, were determined by plotting compound concentration versus T/C values. Mean IC_{50} and IC_{70} values were calculated according to the following formula:

$$n$$

$$\frac{\sum_{X=1}^{3} \log (IC_{70})x}{N}$$

Mean IC_{70} = 10

x = specific tumour cell line

n = total number of cell lines studied

If an IC_{50} or IC_{70} value could not be determined within the examined dose range, the lowest or highest concentration studies was used for the calculation. An assay was considered valuable if the following criteria were fulfilled:

1. Mean number of colonies in the control group dishes for 24-multiwells contained 20 colonies with colony diameters > 50 μm.
2. The positive reference 5-flourouracil (at toxic dose of 1000 μg/ml) must affect colony survival of 30% of controls.

Coefficient of variation in the control group < 50%>

The extracts were tested in several tumour cell lines, for their ability to affect tumour growth. The cell lines tested included: *HT29* colon carcinoma; *SF 268* central nervous system; *GXF 251L* gastric cancer; *LXFE 66NL* epidermoid lung carcinoma; *LXFL 529L* large cell lung carcinoma; *H460* lung adenocarcinoma; *LXFF6 529L* lung adenocarcinoma; *MCF-7* breast cancer; *OVCAR3* ovarian carcinoma; *PC3* prostate carcinoma; *DU145* prostate carcinoma; *RXF 944L* renal cell carcinoma; *MEXF 514L* melanoma; and *MEXF 426NL* melanoma.

The IC50 results are for in vitro studies are presented in Table 1 below:

Cancer Cell Line	Code Cancer Cell Line	IC_{50} μm/ml Incensole	IC_{50} μm/ml Furanogermacren	IC_{50} μm/ml Incensole/ Furanogermacren Mixture	IC_{50} μm/ml 5-Flourouracil
Human Prostate Carcinoma	DU145	ND	ND	5.00	0.021
Human Prostate Carcinoma	PC3	6.00	70.00	1.2	ND
Human Colon Carcinoma	HT29	70.00	70.00	0.9	ND
Human Melanoma	MEXF 514L	ND	ND	0.8	ND
Human Melanoma	MEXF 429NL	ND	ND	20.00	ND

Human Lung Epidermoid Carcinoma	LXFE 66NL	ND	ND	50.00	ND
Human Lung Large Cell Carcinoma	LXFL 529L	ND	ND	4.00	ND
Human Lung Adenocarcinoma	H460	ND	ND	20.00	ND
Human Renal Carcinoma	RXF 944L	ND	ND	30.00	ND
Human Breast Carcinoma	MACL MCF7	ND	ND	7.00	ND
Gastric Carcinoma	GXF 251L	ND	ND	8.00	ND
Ovarian Cancer Xenograft	OVCL OVCAR3	ND	ND	10.00	ND
Carcinoma of the contral nervous system	CNCL SF268	ND	ND	10.00	ND

ND = not determined

Example 2

Antimicrobial activity

These studies were performed to determine the minimum inhibitory concentration (MIC) of incensole/furanogermacren mixture.

MIC values were determined using a macrodilution broth procedure based on NCCLS Documents M7-A3 "Methods for dilution anti-microbial susceptibility tests for bacteria that grow aerobically-third edition, approved standard (1993). The lowest test substance concentration that completely inhibited growth of the test organisms recorded as MIC.

The following organisms were tested:

1. Staphylococcus aureus NCTC 10442
2. Staphylococcus aureus NCTC 6571
3. Enterococcus feacalis NCTC 775

MIC values for incensole/furanogermacren mixture were 100 µg/ml. MIC values for incensole for the above 3 bacterial species was 38 µg/ml causing significant growth retardation.

Pharmaceutically acceptable refers to those properties and/or substances, which are acceptable to the patient from a pharmacological/toxicological point of view including bioavailability and patient acceptance or to the manufacturing chemist

from a physical-chemical point of view regarding composition, formulation, stability and isolatability.

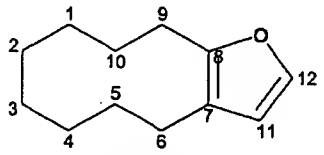
The terms "comprise, comprised and comprising" and the terms "include, included and including" are used interchangeably in this specification and are to be afforded the widest interpretation.

The invention is not limited to the embodiments described above, but may be varied in both construction and detail within the scope of the claims.

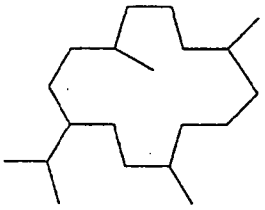
WE CLAIM

1. A composition comprising one or more compound of the present invention, their derivatives, metabolites, analogues and/or mimic molecules with pharmaceutical acceptable additives, diluents, carriers, excipients and pharmaceutical salts thereof.

2. The composition as claimed in claim 1, wherein the compounds of the present invention are selected from the group comprising:



Formula (1)



Formula (2)

wherein for Formula (1)

Bonds between carbons 9-10, 10-1, 1-2, 2-3,3-4, 4-5, 5-6, can be either single or double with the proviso that any two or more double bonds are separated by a single bond.

Compounds also include those containing epoxide rings formed between carbons 9-10, 10-1, 1-2, 2-3,3-4, 4-5 with the proviso that any two or more epoxide rings are separated by a single bond.

wherein for Formula (2)

the carbocyclic ring can have optionally up to 7 endocyclic/exocyclic double bonds with the proviso that any two or more double bonds are separated by single bonds;

Carbon atoms for Formula (1) or (2) can be singly or multiply substituted, optionally and independently by:

an oxo substituent, H, alkyl, aryl, a heterocyclic radical, halogen, alkoxycarbonyl (C1-C5) or carboxyl, hydroxyl, alkoxy (C1-C5), amido, alkyl amido (C1-C5), amino, mono and dialkyl amino (C1-C5), alkyl carbamoyl (C1-C5), thiol, alkylthio (C1-C5);

in addition substituents may form a spiro ring around the carbon atom to which they are attached or they can form fused or bridged rings to adjacent carbon atoms which may be saturated or unsaturated;

Substituents on the aryl or heterocyclic radical are selected from the group consisting essentially of: halogen, alkyl (C1-C5), hydroxyl, alkoxy (C1-C5), alkoxycarbonyl, (C1-C5), carboxyl, amido, alkyl amido (C1-C5), amino, mono and dialkyl amino (C1-C5),alkyl carbamoyl (C1-C5), thiol, alkyl thio (C1-C5) or benzenoid aryl thio, cyano, nitro, haloalkyl (C1-C5), alkIsulfonyl (C1-C5), and sulfonate;

Two of such substituents can be part of a fused ring, which can be either saturated, or unsaturated, heterocyclic or carbo cyclic;

and natural amino acid substituents which may be attached to the compounds of formula (1) or (2) via an ester linkage to a hydroxyl group;

their derivatives, metabolites, analogues and/or mimic molecules with pharmaceutical acceptable additives, diluents, carriers and excipients and pharmaceutically acceptable salts thereof.

3. The composition as claimed in claims 1 or 2, wherein the compounds of the present invention are selected from the group comprising: Incensole, incensole acetate, incensole oxide, incensole oxide acetate, isoincensole, isoincensole

acetate, isoincensole oxide, octyl acetate, octanol, terpinyl acetate, bornyl acetate, trans-ver-benol, verbenone, menthadien-7-ol, terpinen-4-ol, trans-pinocarveol, carvone, borneol, farnesol, farnesene, β-caryophyllene, humulene, β-cadinene, bergamotone, β-guaiene, β-ylangene, β-bourbonene, α-copaene, terpinene, myrcene, ρ-cymene, α- and β-phellandrene, α-thujene, cembrane-A, isocembrane, cembranol, cembranoids, cembranoid alcohols, furanogermacrens, furanogermacrene, germacrene, elemane, cadinene, guaiane, oplopane, eudsmane, echinodol, α-santalene, α-bisabolene, furanodiene, β-santalene, β-bergamotene, β-farnesene, β-bisabolene, SKB4, their derivatives, metabolites, analogues and/or mimic molecules with pharmaceutical acceptable additives, diluents, carriers and excipients and pharmaceutically acceptable salts thereof.

4. The composition as claimed in any preceding claims, wherein the compounds of the present invention are selected from the group comprising at least one of: incensole, incensole acetate, incensole oxide, incensole oxide acetate, isoincensole, isoincensole acetate, isoincensole oxide, and/or at least one of the furanosesquiterpene fumogermacrens, their derivatives, metabolites, analogues and/or mimic molecules with pharmaceutical acceptable additives, diluents, carriers and excipients and pharmaceutically acceptable salts thereof.

5. A pharmaceutical formulation comprising a composition as claimed in any of claims 1 to 4 and a pharmaceutically acceptable carrier thereof.

6. The pharmaceutical formulation as claimed in claim 5, wherein the pharmaceutical carrier is selected from the group comprising cyclodextrin, alpha-cyclodextrin, beta-cyclodextrin, (beta-hydroxypropylcyclodextrin) gamma-cyclodextrin and vitamin E oil.

7. The use of a pharmaceutical formulation for the manufacture of a medicament for treatment of a mammal suffering from a neoplasia comprising a pharmaceutical formulation as claimed in claims 1 to 6.

8. The use of a pharmaceutical formulation as claimed in any of the preceding

claims, wherein the pharmaceutical formulation further includes at least one conventional chemotherapeutic agent.

9. The use of a pharmaceutical formulation as claimed in claim 7, wherein the chemotherapeutic agent is selected from the group comprising flutamide and luprolide, antioestrogens, such as tamoxifen, antimetabolites and cytotoxic agents, such as daunorubicin, flourouracil, floxuridine, interferon alpha, methotrexate, plicamycin, mecaptopurine, thioguanine, adramycin, carmustine, lomustine, cytarabine, cyclophosphamide, doxorubicin, estramustine, altretamine, hydroxyurea, ifosfamide, procarbazine, mutamycin, busulfan, mitoxantrone, carboplatin, cisplatin, streptozocin, bleomycin, dactinomycin and idamycin, hormones such as, medroxyprogesterone, estramustine, ethinyl oestradiol, oestradiol, leuprolide, megestrol, octreotide, diethylstilbestrol, chlorotrianisene, etoposide, podophyllotoxin, and goserelin, nitrogen mustard derivatives such as, melphalan, chlorambucil, methlorethamine and thiotepa, steroids such as, betamethasone, and other antineoplastic agents such as live *Mycobacterium bovis*, dicarbazine, asparaginase, leucovoribn, mitotane, vincristine, vinblastine and texotere, cyclophosphamide, adriamycin, 5-flourouracil, hexamethylmelamine, Acivicin; Aclarubicin; Acodazole Hydrochloride; AcrQnine; Adozelesin; Aldesleukin; Altretamine; Ambomycin; Ametantrone Acetate; Aminoglutethimide; Amsacrine; Anastrozole; Anthramycin; Asparaginase; Asperlin; Azacitidine; Azetepa; Azotomycin; Batimastat; Benzodepa; Bicalutamide; Bisantrene Hydrochloride; Bisnafide Dimesylate; Bizelesin; Bleomycin Sulfate; Brequinar Sodium; Bropirimine; Busulfan; Cactinomycin; Calusterone; Caracemide; Carbetimer; Carboplatin; Carmustine; Carubicin Hydrochloride; Carzelesin; Cedefingol; Chlorambucil; Cirolemycin; Cisplatin; Cladribine; Crisnatol Mesylate; Cyclophosphamide; Cytarabine; Dacarbazine; Dactinomycin; Daunorubicin Hydrochloride; Decitabine; Dexormaplatin; Dezaguanine; Dezaguanine Mesylate; Diaziquone; Docetaxel; Doxorubicin; Doxorubicin Hydrochloride; Droloxifene; Droloxifene Citrate; Dromostanolone Propionate; Duazomycin; Edatrexate; Eflomithine Hydrochloride; Elsamitrucin; Enloplatin; Enpromate; Epipropidine; Epirubicin Hydrochloride; Erbulozole; Esorubicin Hydrochloride; Estramustine;

Estramustine Phosphate Sodium; Etanidazole; Ethiodized Oil I 131; Etoposide; Etoposide Phosphate; Etoprine; Fadrozole Hydrochloride; Fazarabine; Fenretinide; Floxuridine; Fludarabine Phosphate; Fluorouracil; Flurocitabine; Fosquidone; Fostriecin Sodium; Gemcitabine; Gemcitabine Hydrochloride; Gold Au 198; Hydroxyurea; Idarubicin Hydrochloride; Ifosfamide; Ilmofosine; Interferon Alfa-2a; Interferon Alfa-2b; Interferon Alfa-n1; Interferon Alfa-n3; Interferon Beta- I a; Interferon Gamma- I b; Iproplatin; Irinotecan Hydrochloride; Lanreotide Acetate; Letrozole; Leuprolide Acetate; Liarozole Hydrochloride; Lometrexol Sodium; Lomustine; Losoxantrone Hydrochloride; Masoprocol; Maytansine; Mechlorethamine Hydrochloride; Megestrol Acetate; Melengestrol Acetate; Melphalan; Menogaril; Mercaptopurine; Methotrexate; Methotrexate Sodium; Metoprine; Meturedepa; Mitindomide; Mitocarcin; Mitocromin; Mitogillin; Mitomalcin; Mitomycin; Mitosper; Mitotane; Mitoxantrone Hydrochloride; Mycophenolic Acid; Nocodazole; Nogalamycin; Ormaplatin; Oxisuran; Paclitaxel; Pegaspargase; Peliomycin; Pentamustine; Peplomycin Sulfate; Perfosfamide; Pipobroman; Piposulfan; Piroxantrone Hydrochloride; Plicamycin; Plomestane; Porfimer Sodium; Porfiromycin; Prednimustine; Procarbazine Hydrochloride; Puromycin; Puromycin Hydrochloride; Pyrazofurin; Riboprine; Rogletimide; Safmgol; Safingol Hydrochloride; Semustine; Simtrazene; Sparfosate Sodium; Sparsomycin; Spirogermanium Hydrochloride; Spiromustine; Spiroplatin; Streptonigrin; Streptozocin; Strontium Chloride Sr 89; Sulofenur; Talisomycin; Taxane; Taxoid; Tecogalan Sodium; Tegafur; Teloxantrone Hydrochloride; Temoporfin; Teniposide; Teroxirone; Testolactone; Thiamiprine; Thioguanine; Thiotepa; Tiazofurin; Tirapazamine; Topotecan Hydrochloride; Toremifene Citrate; Trestolone Acetate; Triciribine Phosphate; Trimetrexate; Trimetrexate Glucuronate; Triptorelin; Tubulozole Hydrochloride; Uracil Mustard; Uredepa; Vapreotide; Verteporfin; Vinblastine Sulfate; Vincristine Sulfate; Vindesine; Vindesine Sulfate; Vinepidine Sulfate; Vinglycinate Sulfate; Vinleurosine Sulfate; Vinorelbine Tartrate; Vinrosidine Sulfate; Vinzolidine Sulfate; Vorozole; Zeniplatin; Zinostatin; Zorubicin Hydrochloride, 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid;

amrubicin; atrsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; DHEA; bromineepiandrosterone; epiandrosterone; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocannycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; fmasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone;

ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; irinotecan; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maltansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A +myobacterium cell wall sk; mopidamol; multiple drug resistance genie inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone +pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; propyl bis-acridone;

prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfmosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thalidomide; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene dichloride; topotecan; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; venom, anti-venom, veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, immunostimulating drugs or therapeutic agents, their metabolites, salts and derivatives thereof .

10. The use of a pharmaceutical formulation as claimed in claims 7 to 9, wherein the pharmaceutical formulation is administered in combination with radiation treatment.

11. The use of a pharmaceutical formulation as claimed in claims 7 to 10, wherein the pharmaceutical formulation is administered in combination with surgery.

12. The use of a pharmaceutical formulation as claimed in claims 7 to 11, wherein the neoplasia is a precancerous lesion including syndromes represented by abnormal neoplastic and/or dysplastic, changes of tissue comprising precancerous growths in colonic, breast, renal, central nervous, gastric, or lung tissues, or conditions such as dysplastic nevus syndrome, a precursor to malignant melanoma of the skin, dysplastic nevus syndromes, polyposis syndromes, colonic polyps, precancerous lesions of the cervix (i.e., cervical dysplasia), prostatic dysplasia, bronchial dysplasia, breast, bladder and/or skin and related conditions (e.g., actinic keratosis), whether the lesions are clinically identifiable or not.

13. The use of a pharmaceutical formulation as claimed in claims 7 to 12, wherein the neoplasia is prostate cancer, colon cancer, small cell lung cancer, large cell lung cancer, lung adenocarcinoma, epidermoid lung cancer, melanoma (including amelanotic subtypes), renal cell carcinoma, gastric carcinoma, cancers of the central nervous system including brain tumours, neuroblastomas, gastric carcinoma, breast cancer, ovarian cancer, testicular cancer, lymphoma and leukaemia, oesophageal cancer, stomach cancer, liver cancers, prostate cancer, cervical cancer, adrenal cancer, oral or mucosal cancer, bladder cancer, pancreatic cancer, lymphoma, Hodgkins disease, sarcomas. Hematopoeitic cell cancers such as B cell leukaemia/lymphomas, myelomas, T-cell leukemias/lymphomas, small cell leukemias/lymphomas, null cell, sezary, monocytic, myelomonocytic and Hairy cell leukemias.

14. The use of a pharmaceutical formulation as claimed in claims 7 to 13, wherein the neoplasia is in the form of a tumour comprising an epidermoid and myeloid tumour, acute or chronic, nonsmall cell, squamous or solid.

15. The use of a pharmaceutical formulation as claimed in claims 7 to 14, wherein the composition is micronized.

16. The use of a pharmaceutical formulation as claimed in claims 7 to 15, wherein the pharmaceutical formulation has an enteric coating.

17. The use of a pharmaceutical formulation as claimed in claim 16, wherein the enteric coating is made of a polymer or copolymer.

18. The use of a pharmaceutical formulation as claimed in claim 17, wherein the polymer or copolymer is selected from the group consisting of poly(lactic-glycolic acid) polyester, cellulose acetate phthalate, hydroxypropyl-methyl cellulose phthalate poly(butyl methacrylate), (2-dimethyl aminoethyl) methacrylate, and methyl methacrylate.

19. The use of a pharmaceutical formulation as claimed in claims 7 to 18, wherein, the pharmaceutical formulation is administered enterally, parenterally, topically, orally, sub-lingually, rectally, nasally or vaginally.

20. The use of a pharmaceutical formulation as claimed in claims 7 to 19, wherein the composition is formulated into liposomes or carbohydrate vehicles.

21. The use of a pharmaceutical formulation as claimed in claim 20, wherein the liposomes or carbohydrate vehicles are specifically targeted to tumours by covalently attaching a monoclonal antibody directed to a tumour-associated antigen.

22. The use of a pharmaceutical formulation as clalmed in claims 7 to 21, wherein the pharmaceutical formulation is administered intermittently.

23. The use of a pharmaceutical formulation as claimed in claims 7 to 22, wherein the pharmaceutical formulation is a unlt dose that comprises 5-500 mg of active

ingredient consisting of at least one compound of the present invention.

24. The use of a pharmaceutical formulation as claimed in claims 7 to 23, wherein the pharmaceutical formulation is administered to a mammal.

25. The use of a pharmaceutical formulation as claimed in claim 24, wherein said mammal is a neonate and said administering is effected prior to delivery of said neonate and/or during delivery of said neonate.

26. The use of a pharmaceutical formulation as claimed in claims 7 to 25, wherein said compounds of the present invention acts as a prodrug.

27. The use of a pharmaceutical formulation for the manufacture of a medicament for treatment of a mammal suffering from an immunodysregulatory condition comprising a composition as claimed in claims 1 to 6, to a subject.

28. The use of a pharmaceutical formulation as claimed in claim 27, wherein the immunodysregulation condition is caused by a viral infection, intracellular bacterial infection, extracellular bacterial infection, fungal infection, yeast infection, extracellular parasite infection, intracellular parasite infection, protozoan parasite, multicellular parasite, autoimmune disease, immunosuppressive therapy, chemotherapy, anti-infective agent therapy, wound, burn, the presence of an immunosuppressive molecule, gastrointestinal irritation or any combination of the foregoing is selected from (a) a DNA virus infection or an RNA virus(b) a parasite infection, a *Trypanosoma*, *Plasmodium*, *Cryptosporidium*, *Entamoeba*, *Balantidium*, *Leishmania*, *Pneumocystis*, *Trichomoniasis* or *Toxoplasma* infection, wherein the *Trypanosoma*, *Plasmodium*, *Cryptosporidium*, *Entamoeba*, *Balantidium*, *Leishmania*, *Pneumocystis*, *Trichomoniasis* or *Toxoplasma* infection is selected from but not limited to *Trypanosoma cruzi*, *Trypanosoma brucei*, *Trypanosoma gambiense*, *Trypanosoma rhodesiense*, *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, *Plasmodium ovale*, *Plasmodium berghei*, *Entamoeba histolytica*, *Balantidium coli*, *Leishmania brazilienis*, *Leishmania mexicana*,

Leishmania donovani, Leishmania tropica, Pneumocystis carinii, Trichomoniasis vaginalis, and *Toxoplasma gondii* (c) a mycoplasma infection, a *Listeria* infection or a *Mycobacterium* infection; (d) a *Streptococcus* infection, a *Staphylococcus* infection, a *Vibrio* infection, a *Salmonella* infection; a *Shigella* infection, an enterotoxigenic, enteropathogenic, enteroinvasive or enterohemorrhagic *E. coli* infection, a *Yersinia* infection, a *Campylobacter* infection, a *Pseudomonas* infection, a *Borrelia* infection, a *Legionella* infection and a *Haemophilus* infection; (e) pulmonary *Aspergillosis*, mucosal or oropharyngealcandidiasis and juvenile paracoccidiomyosis; (f) a *Candida* infection and a *Cryptococcus* infection; (g) systemic lupus erythematosis, arthritis, asthma, and diabetes (h) adriamycin treatment, cisplatin treatment, mitomycin C treatment, amphoteracin B treatment; (i) a gamma-radiation treatment; (j) nucleoside analog treatment for viral infection or for cancer; (k) surgical and accidental wounds, septic shock caused by surgery; (l) cyclosporin treatment and corticosteroid treatment; (m) Irritable bowel treatment, Crohn's disease, wasting syndrome, cachexia, Motor Neuron disease, Multiple Sclerosis, inflammatory bowel disease, respiratory distress syndrome, chronic diarrhoea; (n) cancer; (o) cirrhoisis; (p) gram positive multi-drug resistant bacteria or (q) any combination of (a) through (p).

29. The use of a pharmaceutical formulation as claimed in claim 28, wherein the DNA virus infection or the RNA virus infection is selected from a retrovirus infection, a togavirus infection, a flavivirus infection, a rubivirus infection, a pestivirus infection, a lipid envelope virus infection, a filovirus, a picornavirus infection, a rhinovirus infection, a coronavirus infection, a respiratory syncytial virus infection, a poliovirus infection, a parainfluenza virus infection, influenza virus infection, hantavirus, adeno-associated virus, measles virus, poxvirus, filovirus, human papilloma virus and animal papilloma virus infection.

30. The use of a pharmaceutical formulation as claimed in claims 27 to 29, wherein the composition further includes at least one conventional chemotherapeutic agent.

31. The pharmaceutical formulation as claimed in claim 30, wherein the chemotherapeutic agent is selected from the group comprising flutamide and luprolide, antioestrogens, such as tamoxifen, antimetabolites and cytotoxic agents, such as daunorubicin, flourouracil, floxuridine, interferon alpha, methotrexate, plicamycln, mecaptopurine, thioguanine, adramycin, carmustine, lomustine, cytarabine, cyclophosphamide, doxorubicin, estramustine, altretamine, hydroxyurea, ifosfamide, procarbazine, mutamycin, busulfan, mitoxantrone, carboplatin, cisplatin, streptozocin, bleomycin, dactinomycin and idamycin, hormones such as, medroxyprogesterone, estramustine, ethinyl oestradiol, oestradiol, leuprolide, megestrol, octreotide, diethylstilbestrol, chlorotrianisene, etoposide, podophyllotoxin, and goserelin, nitrogen mustard derivatives such as, melphalan, chlorambucil, methlorethamine and thiotepa, steroids such as, betamethasone, and other antineoplastic agents such as live *Mycobacterium bovis*, dicarbazine, asparaginase, leucovoribn, mitotane, vincristine, vinblastine and texotere, cyclophosphamide, adriamycin, 5-flourouracil, hexamethylmelamine, Acivicin; Aclarubicin; Acodazole Hydrochloride; AcrQnine; Adozelesin; Aldesleukin; Altretamine; Ambomycin; Ametantrone Acetate; Aminoglutethimide; Amsacrine; Anastrozole; Anthramycin; Asparaginase; Asperlin; Azacitidine; Azetepa; Azotomycin; Batimastat; Benzodepa; Bicalutamide; Bisantrene Hydrochloride; Bisnafide Dimesylate; Bizelesin; Bleomycin Sulfate; Brequinar Sodium; Bropirimine; Busulfan; Cactinomycin; Calusterone; Caracemide; Carbetimer; Carboplatin; Carmustine; Carubicin Hydrochloride; Carzelesin; Cedefingol; Chlorambucil; Cirolemycin; Cisplatin; Cladribine; Crisnatol Mesylate; Cyclophosphamide; Cytarabine; Dacarbazine; Dactinomycin; Daunorubicin Hydrochloride; Decitabine; Dexormaplatin; Dezaguanine; Dezaguanine Mesylate; Diaziquone; Docetaxel; Doxorubicin; Doxorubicin Hydrochloride; Droloxifene; Droloxifene Citrate; Dromostanolone Propionate; Duazomycin; Edatrexate; Eflomithine Hydrochloride; Elsamitrucin; Enloplatin; Enpromate; Epipropidine; Epirubicin Hydrochloride; Erbulozole; Esorubicin Hydrochloride; Estramustine; Estramustine Phosphate Sodium; Etanidazole; Ethiodized Oil I 131; Etoposide; Etoposide Phosphate; Etoprine; Fadrozole Hydrochloride; Fazarabine; Fenretlnide; Floxuridine; Fludarabine Phosphate; Fluorouracil; Flurocitabine;

Fosquidone; Fostriecin Sodium; Gemcitabine; Gemcitabine Hydrochloride; Gold Au 198; Hydroxyurea; Idarubicin Hydrochloride; Ifosfamide; Ilmofosine; Interferon Alfa-2a; Interferon Alfa-2b; Interferon Alfa-n1; Interferon Alfa-n3; Interferon Beta- I a; Interferon Gamma- I b; Iproplatin; Irinotecan Hydrochloride; Lanreotide Acetate; Letrozole; Leuprolide Acetate; Liarozole Hydrochloride; Lometrexol Sodium; Lomustine; Losoxantrone Hydrochloride; Masoprocol; Maytansine; Mechlorethamine Hydrochloride; Megestrol Acetate; Melengestrol Acetate; Melphalan; Menogaril; Mercaptopurine; Methotrexate; Methotrexate Sodium; Metoprine; Meturedepa; Mitindomide; Mitocarcin; Mitocromin; Mitogillin; Mitomalcin; Mitomycin; Mitosper; Mitotane; Mitoxantrone Hydrochloride; Mycophenolic Acid; Nocodazole; Nogalamycin; Ormaplatin; Oxisuran; Paclitaxel; Pegaspargase; Peliomycin; Pentamustine; Peplomycin Sulfate; Perfosfamide; Pipobroman; Piposulfan; Piroxantrone Hydrochloride; Plicamycin; Plomestane; Porfimer Sodium; Porfiromycin; Prednimustine; Procarbazine Hydrochloride; Puromycin; Puromycin Hydrochloride; Pyrazofurin; Riboprine; Rogletimide; Safmgol; Safingol Hydrochloride; Semustine; Simtrazene; Sparfosate Sodium; Sparsomycin; Spirogermanium Hydrochloride; Spiromustine; Spiroplatin; Streptonigrin; Streptozocin; Strontium Chloride Sr 89; Sulofenur; Talisomycin; Taxane; Taxoid; Tecogalan Sodium; Tegafur; Teloxantrone Hydrochloride; Temoporfin; Teniposide; Teroxirone; Testolactone; Thiamiprine; Thioguanine; Thiotepa; Tiazofurin; Tirapazamine; Topotecan Hydrochloride; Toremifene Citrate; Trestolone Acetate; Triciribine Phosphate; Trimetrexate; Trimetrexate Glucuronate; Triptorelin; Tubulozole Hydrochloride; Uracil Mustard; Uredepa; Vapreotide; Verteporfin; Vinblastine Sulfate; Vincristine Sulfate; Vindesine; Vindesine Sulfate; Vinepidine Sulfate; Vinglycinate Sulfate; Vinleurosine Sulfate; Vinorelbine Tartrate; Vinrosidine Sulfate; Vinzolidine Sulfate; Vorozole; Zeniplatin; Zinostatin; Zorubicin Hydrochloride, 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; atrsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; DHEA; bromineepiandrosterone; epiandrosterone; antarelix; anti-dorsalizing morphogenetic protein-1;

antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives; beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; dacliximab; decitabine; dehydrodidemnin B; deslorelin; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocannycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflomithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; fmasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; irinotecan; iroplact;

irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol; lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A +myobacterium cell wall sk; mopidamol; multiple drug resistance genie inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone +pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors;

purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras farnesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdl 1 mimetics; semustine; senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfmosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thalidomide; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene dichloride; topotecan; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; venom, anti-venom, veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, immunostimulating drugs or therapeutic agents, their metabolites, salts and derivatives thereof .

32. The use of a pharmaceutical formulation as claimed in claims 27 to 31, wherein the composition further includes at least one anti-viral agent.

33. The use of a pharmaceutical formulation as claimed in claim 32, wherein the

anti-viral agents are selected from the group comprising nucleoside analogues (AZT; ddC; ddI; d4T; 3TC; BW 1592; PMEA/bis-POM PMEA; dOTC; DAPD); non-nucleoside reverse transcriptase inhibitors (delavirdine; DMP 266; HBY097; loviride; nevirapine, emivirine; AG1549; PNU142721; Calanolide A; DPC961); protease inhibitors (ABT-378; ritonavir; nelfinavir; BW 141; KNI-272; indinavir; saquinavir; L-756,423; DMP-450; BMS-232630); ALX40-4C; hydroxyurea; lobucavir; pentafuside; T-1249; PRO 542; FP-21399; AMD 3100; HE-2000 and peptide T; Abacavir; Acemannan; Acyclovir; Acyclovir Sodium; Adefovir; Alovudine; Alvircept Sudotox; Amantadine Hydrochloride; Aranotin; Arildone; Atevirdine Mesylate; Avridine; Cidofovir; Cipamfylline; Coviracil; Cytarabine Hydrochloride; Delavirdine Mesylate; Desciclovir; Didanosine; Disoxaril; Edoxudine; Emivirine; Emtricitabine; Enviradene; Enviroxime; Epivir; Famciclovir; Famotine Hydrochloride; Fiacitabine; Fialuridine; Fosarilate; Foscarnet Sodium; Fosfonet Sodium; Ganciclovir; Ganciclovir Sodium; Idoxuridine; Indinavir; Kethoxal; Lamivudine; Lobucavir; Lodenosine; Lopinavir, Memotine Hydrochloride; Methisazone; Nelfinavir; Nevirapine; Penciclovir; Pirodavir; Ribavirin; Rimantadine Hydrochloride; Saquinavir Mesylate; Ritonavir; Somantadine Hydrochloride; Sorivudine; Statolon; Stavudine; Tenofovir; Tilorone Hydrochloride; Trifluridine; Valacyclovir Hydrochloride; Vidarabine; Vidarabine Phosphate; Vidarabine Sodium Phosphate; Tipranavir, Viroxime; Zalcitabine; Zidovudine; Zinviroxime and Interferon.

34. The use of a pharmaceutical formulation as claimed in claims 27 to 33, wherein the composition further includes at least one anti-parasite agent.

35. The use of a pharmaceutical formulation as claimed in claim 34, wherein the anti-parasite agents are selected from the group comprising chloroquin, primaquine, mefloquine, pyrimethamine-sulfadoxone, atoraquone/dapsone; halofantrine; artemisinin derivatives; atoraquone + proguanol, co-artemether; podophyllotoxin; pentamidine, diloxanide furoate, metronidazole, tindazole, tetracycline, quinacrine, stibogluconate, amphotericin B, quinine, doxycline, trimethoprim-sulfamethoxazole, metronidazole, nifurtimox, suramin,

melarsoprol, benznidazole, their metabolites, salts derivatives or any other anti-parasitic agent thereof .

36. The use of a pharmaceutical formulation as claimed in claims 27 to 35, wherein the composition is micronized.

37. The use of a pharmaceutical formulation as claimed in claims 27 to 36, wherein the composition enhances endogenous hsp levels.

38. The use of a pharmaceutical formulation as claimed in claims 27 to 37, wherein the composition enhances endogenous precursor dendritic cell levels.

39. The use of a pharmaceutical formulation as claimed in claims 27 to 38, wherein the pharmaceutical formulation has an enteric coating.

40. The use of a pharmaceutical formulation as claimed in claim 39, wherein the enteric coating is made of a polymer or copolymer.

41. The use of a pharmaceutical formulation as claimed in claim 40 wherein the polymer or copolymer is selected from the group consisting of poly(lactic-glycolic acid) polyester, cellulose acetate phthalate, hydroxypropyl-methyl cellulose phthalate poly(butyl methacrylate), (2-dimethyl aminoethyl) methacrylate, and methyl methacrylate.

42. The use of a pharmaceutical formulation as claimed in claims 27 to 41, wherein the pharmaceutical formulation is administered enterally, parenterally, topically, orally, rectally, nasally or vaginally.

43. The use of a pharmaceutical formulation as claimed in claims 27 to 42, wherein the composition is formulated into liposomes or carbohydrate vehicles.

44. The use of a pharmaceutical formulation as claimed in claim 43, wherein the liposomes or carbohydrate vehicles are targeted to HIV Infected cells by putting

viral antibodies on its surface.

45. The use of a pharmaceutical formulation as claimed in claim 44, wherein the viral antibodies are directed to the HIV coat protein gp160 and/or gp120.

46. The use of a pharmaceutical formulation as claimed in claims 27 to 45, wherein the pharmaceutical formulation is administered intermittently.

47. The use of a pharmaceutical formulation as claimed in claims 27 to 46, wherein the pharmaceutical formulation is administered to a mammal.

48. The use of a pharmaceutical formulation as claimed in claim 47, wherein said mammal is a neonate and said administering is effected prior to delivery of said neonate and/or during delivery of said neonate.

49. The use of a pharmaceutical formulation as claimed in claims 27 to 48, wherein said compounds of the present invention acts as a prodrug.

50. The use of a pharmaceutical formulation for the manufacture of a medicament for sensitising a resistant neoplasia to subsequent therapy comprising administering to a patient in need thereof a therapeutically effective amount of composition as claimed in claims 1 to 6.

51. The use of a pharmaceutical formulation as claimed in claim 50, wherein the pharmaceutical formulation further includes at least one conventional chemotherapeutic agent.

52. The use of a pharmaceutical formulation as claimed in claim 51, wherein the chemotherapeutic agent is selected from the group comprising flutamide and luprolide, antioestrogens, such as tamoxifen, antimetabolites and cytotoxic agents, such as daunorubicin, flourouracil, floxuridine, interferon alpha, methotrexate, plicamycin, mecaptopurine, thioguanine, adramycin, carmustine, lomustine, cytarabine, cyclophosphamide, doxorubicin, estramustine,

altretamine, hydroxyurea, Ifosfamide, procarbazine, mutamycin, busulfan, mitoxantrone, carboplatin, cisplatin, streptozocin, bleomycin, dactinomycin and idamycin, hormones such as, medroxyprogesterone, estramustine, ethinyl oestradiol, oestradiol, leuprolide, megestrol, octreotide, diethylstilbestrol, chlorotrianisene, etoposide, podophyllotoxin, and goserelin, nitrogen mustard derivatives such as, melphalan, chlorambucil, methlorethamine and thiotepa, steroids such as, betamethasone, and other antineoplastic agents such as live *Mycobacterium bovis*, dicarbazine, asparaginase, leucovorbn, mitotane, vincristine, vinblastine and texotere, cyclophosphamide, adriamycin, 5-flourouracil, hexamethylmelamine, Acivicin; Aclarubicin; Acodazole Hydrochloride; AcrQnine; Adozelesin; Aldesleukin; Altretamine; Ambomycin; Ametantrone Acetate; Aminoglutethimide; Amsacrine; Anastrozole; Anthramycin; Asparaginase; Asperlin; Azacitidine; Azetepa; Azotomycin; Batimastat; Benzodepa; Bicalutamide; Bisantrene Hydrochloride; Bisnafide Dimesylate; Bizelesin; Bleomycin Sulfate; Brequinar Sodium; Bropirimine; Busulfan; Cactinomycin; Calusterone; Caracemide; Carbetimer; Carboplatin; Carmustine; Carubicin Hydrochloride; Carzelesin; Cedefingol; Chlorambucil; Cirolemycin; Cisplatin; Cladribine; Crisnatol Mesylate; Cyclophosphamide; Cytarabine; Dacarbazine; Dactinomycin; Daunorubicin Hydrochloride; Decitabine; Dexormaplatin; Dezaguanine; Dezaguanine Mesylate; Diaziquone; Docetaxel; Doxorubicin; Doxorubicin Hydrochloride; Droloxifene; Droloxifene Citrate; Dromostanolone Propionate; Duazomycin; Edatrexate; Eflomithine Hydrochloride; Elsamitrucin; Enloplatin; Enpromate; Epipropidine; Epirubicin Hydrochloride; Erbulozole; Esorubicin Hydrochloride; Estramustine; Estramustine Phosphate Sodium; Etanidazole; Ethiodized Oil I 131; Etoposide; Etoposide Phosphate; Etoprine; Fadrozole Hydrochloride; Fazarabine; Fenretinide; Floxuridine; Fludarabine Phosphate; Fluorouracil; Flurocitabine; Fosquidone; Fostriecin Sodium; Gemcitabine; Gemcitabine Hydrochloride; Gold Au 198; Hydroxyurea; Idarubicin Hydrochloride; Ifosfamide; Ilmofosine; Interferon Alfa-2a; Interferon Alfa-2b; Interferon Alfa-n1; Interferon Alfa-n3; Interferon Beta- I a; Interferon Gamma- I b; Iproplatin; Irinotecan Hydrochloride; Lanreotide Acetate; Letrozole; Leuprolide Acetate; Liarozole Hydrochloride; Lometrexol Sodium; Lomustine; Losoxantrone Hydrochloride; Masoprocol;

Maytansine; Mechlorethamine Hydrochloride; Megestrol Acetate; Melengestrol Acetate; Melphalan; Menogaril; Mercaptopurine; Methotrexate; Methotrexate Sodium; Metoprine; Meturedepa; Mitindomide; Mitocarcin; Mitocromin; Mitogillin; Mitomalcin; Mitomycin; Mitosper; Mitotane; Mitoxantrone Hydrochloride; Mycophenolic Acid; Nocodazole; Nogalamycin; Ormaplatin; Oxisuran; Paclitaxel; Pegaspargase; Peliomycin; Pentamustine; Peplomycin Sulfate; Perfosfamide; Pipobroman; Piposulfan; Piroxantrone Hydrochloride; Plicamycin; Plomestane; Porfimer Sodium; Porfiromycin; Prednimustine; Procarbazine Hydrochloride; Puromycin; Puromycin Hydrochloride; Pyrazofurin; Riboprine; Rogletimide; Safmgol; Safingol Hydrochloride; Semustine; Simtrazene; Sparfosate Sodium; Sparsomycin; Spirogermanium Hydrochloride; Spiromustine; Spiroplatin; Streptonigrin; Streptozocin; Strontium Chloride Sr 89; Sulofenur; Talisomycin; Taxane; Taxoid; Tecogalan Sodium; Tegafur; Teloxantrone Hydrochloride; Temoporfin; Teniposide; Teroxirone; Testolactone; Thiamiprine; Thioguanine; Thiotepa; Tiazofurin; Tirapazamine; Topotecan Hydrochloride; Toremifene Citrate; Trestolone Acetate; Triciribine Phosphate; Trimetrexate; Trimetrexate Glucuronate; Triptorelin; Tubulozole Hydrochloride; Uracil Mustard; Uredepa; Vapreotide; Verteporfin; Vinblastine Sulfate; Vincristine Sulfate; Vindesine; Vindesine Sulfate; Vinepidine Sulfate; Vinglycinate Sulfate; Vinleurosine Sulfate; Vinorelbine Tartrate; Vinrosidine Sulfate; Vinzolidine Sulfate; Vorozole; Zeniplatin; Zinostatin; Zorubicin Hydrochloride, 20-epi-1,25 dihydroxyvitamin D3; 5-ethynyluracil; abiraterone; aclarubicin; acylfulvene; adecypenol; adozelesin; aldesleukin; ALL-TK antagonists; altretamine; ambamustine; amidox; amifostine; aminolevulinic acid; amrubicin; atrsacrine; anagrelide; anastrozole; andrographolide; angiogenesis inhibitors; antagonist D; antagonist G; DHEA; bromineeplandrosterone; epiandrosterone; antarelix; anti-dorsalizing morphogenetic protein-1; antiandrogen, prostatic carcinoma; antiestrogen; antineoplaston; antisense oligonucleotides; aphidicolin glycinate; apoptosis gene modulators; apoptosis regulators; apurinic acid; ara-CDP-DL-PTBA; arginine deaminase; asulacrine; atamestane; atrimustine; axinastatin 1; axinastatin 2; axinastatin 3; azasetron; azatoxin; azatyrosine; baccatin III derivatives; balanol; batimastat; BCR/ABL antagonists; benzochlorins; benzoylstaurosporine; beta lactam derivatives;

beta-alethine; betaclamycin B; betulinic acid; bFGF inhibitor; bicalutamide; bisantrene; bisaziridinylspermine; bisnafide; bistratene A; bizelesin; breflate; bropirimine; budotitane; buthionine sulfoximine; calcipotriol; calphostin C; camptothecin derivatives; canarypox IL-2; capecitabine; carboxamide-amino-triazole; carboxyamidotriazole; CaRest M3; CARN 700; cartilage derived inhibitor; carzelesin; casein kinase inhibitors (ICOS); castanospermine; cecropin B; cetrorelix; chlorins; chloroquinoxaline sulfonamide; cicaprost; cis-porphyrin; cladribine; clomifene analogues; clotrimazole; collismycin A; collismycin B; combretastatin A4; combretastatin analogue; conagenin; crambescidin 816; crisnatol; cryptophycin 8; cryptophycin A derivatives; curacin A; cyclopentanthraquinones; cycloplatam; cypemycin; cytarabine ocfosfate; cytolytic factor; cytostatin; daclixímab; decitabine; dehydrodidemnin B; deslorelin; dexifosfamide; dexrazoxane; dexverapamil; diaziquone; didemnin B; didox; diethylnorspermine; dihydro-5-azacytidine; dihydrotaxol, 9-; dioxamycin; diphenyl spiromustine; docosanol; dolasetron; doxifluridine; droloxifene; dronabinol; duocannycin SA; ebselen; ecomustine; edelfosine; edrecolomab; eflornithine; elemene; emitefur; epirubicin; epristeride; estramustine analogue; estrogen agonists; estrogen antagonists; etanidazole; etoposide phosphate; exemestane; fadrozole; fazarabine; fenretinide; filgrastim; fmasteride; flavopiridol; flezelastine; fluasterone; fludarabine; fluorodaunorunicin hydrochloride; forfenimex; formestane; fostriecin; fotemustine; gadolinium texaphyrin; gallium nitrate; galocitabine; ganirelix; gelatinase inhibitors; gemcitabine; glutathione inhibitors; hepsulfam; heregulin; hexamethylene bisacetamide; hypericin; ibandronic acid; idarubicin; idoxifene; idramantone; ilmofosine; ilomastat; imidazoacridones; imiquimod; immunostimulant peptides; insulin-like growth factor-1 receptor inhibitor; interferon agonists; interferons; interleukins; iobenguane; iododoxorubicin; ipomeanol, 4-; irinotecan; iroplact; irsogladine; isobengazole; isohomohalicondrin B; itasetron; jasplakinolide; kahalalide F; lamellarin-N triacetate; lanreotide; leinamycin; lenograstim; lentinan sulfate; leptolstatin; letrozole; leukemia inhibiting factor; leukocyte alpha interferon; leuprolide+estrogen+progesterone; leuprorelin; levamisole; liarozole; linear polyamine analogue; lipophilic disaccharide peptide; lipophilic platinum compounds; lissoclinamide 7; lobaplatin; lombricine; lometrexol;

lonidamine; losoxantrone; lovastatin; loxoribine; lurtotecan; lutetium texaphyrin; lysofylline; lytic peptides; maitansine; mannostatin A; marimastat; masoprocol; maspin; matrilysin inhibitors; matrix metalloproteinase inhibitors; menogaril; merbarone; meterelin; methioninase; metoclopramide; MIF inhibitor; mifepristone; miltefosine; mirimostim; mismatched double stranded RNA; mitoguazone; mitolactol; mitomycin analogues; mitonafide; mitotoxin fibroblast growth factor-saporin; mitoxantrone; mofarotene; molgramostim; monoclonal antibody, human chorionic gonadotrophin; monophosphoryl lipid A +myobacterium cell wall sk; mopidamol; multiple drug resistance genie inhibitor; multiple tumor suppressor 1-based therapy; mustard anticancer agent; mycaperoxide B; mycobacterial cell wall extract; myriaporone; N-acetyldinaline; N-substituted benzamides; nafarelin; nagrestip; naloxone +pentazocine; napavin; naphterpin; nartograstim; nedaplatin; nemorubicin; neridronic acid; neutral endopeptidase; nilutamide; nisamycin; nitric oxide modulators; nitroxide antioxidant; nitrullyn; O6-benzylguanine; octreotide; okicenone; oligonucleotides; onapristone; ondansetron; ondansetron; oracin; oral cytokine inducer; ormaplatin; osaterone; oxaliplatin; oxaunomycin; paclitaxel analogues; paclitaxel derivatives; palauamine; palmitoylrhizoxin; pamidronic acid; panaxytriol; panomifene; parabactin; pazelliptine; pegaspargase; peldesine; pentosan polysulfate sodium; pentostatin; pentrozole; perflubron; perfosfamide; perillyl alcohol; phenazinomycin; phenylacetate; phosphatase inhibitors; picibanil; pilocarpine hydrochloride; pirarubicin; piritrexim; placetin A; placetin B; plasminogen activator inhibitor; platinum complex; platinum compounds; platinum-triamine complex; porfimer sodium; porfiromycin; propyl bis-acridone; prostaglandin J2; proteasome inhibitors; protein A-based immune modulator; protein kinase C inhibitor; protein kinase C inhibitors, microalgal; protein tyrosine phosphatase inhibitors; purine nucleoside phosphorylase inhibitors; purpurins; pyrazoloacridine; pyridoxylated hemoglobin polyoxyethylene conjugate; raf antagonists; raltitrexed; ramosetron; ras famesyl protein transferase inhibitors; ras inhibitors; ras-GAP inhibitor; retelliptine demethylated; rhenium Re 186 etidronate; rhizoxin; ribozymes; RII retinamide; rogletimide; rohitukine; romurtide; roquinimex; rubiginone B1; ruboxyl; safingol; saintopin; SarCNU; sarcophytol A; sargramostim; Sdi 1 mimetics; semustine;

senescence derived inhibitor 1; sense oligonucleotides; signal transduction inhibitors; signal transduction modulators; single chain antigen binding protein; sizofiran; sobuzoxane; sodium borocaptate; sodium phenylacetate; solverol; somatomedin binding protein; sonermin; sparfosic acid; spicamycin D; spiromustine; splenopentin; spongistatin 1; squalamine; stem cell inhibitor; stem-cell division inhibitors; stipiamide; stromelysin inhibitors; sulfmosine; superactive vasoactive intestinal peptide antagonist; suradista; suramin; swainsonine; synthetic glycosaminoglycans; tallimustine; tamoxifen methiodide; tauromustine; tazarotene; tecogalan sodium; tegafur; tellurapyrylium; telomerase inhibitors; temoporfin; temozolomide; teniposide; tetrachlorodecaoxide; tetrazomine; thaliblastine; thalidomide; thiocoraline; thrombopoietin; thrombopoietin mimetic; thymalfasin; thymopoietin receptor agonist; thymotrinan; thyroid stimulating hormone; tin ethyl etiopurpurin; tirapazamine; titanocene dichloride; topotecan; topsentin; toremifene; totipotent stem cell factor; translation inhibitors; tretinoin; triacetyluridine; triciribine; trimetrexate; triptorelin; tropisetron; turosteride; tyrosine kinase inhibitors; tyrphostins; UBC inhibitors; ubenimex; urogenital sinus-derived growth inhibitory factor; urokinase receptor antagonists; vapreotide; variolin B; vector system, erythrocyte gene therapy; velaresol; venom, anti-venom, veramine; verdins; verteporfin; vinorelbine; vinxaltine; vitaxin; vorozole; zanoterone; zeniplatin; zilascorb; zinostatin stimalamer, immunostimulating drugs or therapeutic agents, their metabolites, salts and derivatives thereof .

53. The use of a pharmaceutical formulation as claimed in claims 50 to 52, wherein the pharmaceutical formulation is administered in combination with radiation treatment.

54. The use of a pharmaceutical formulation as claimed in claims 50 to 53, wherein the pharmaceutical formulation is administered in combination with surgery.

55. The use of a pharmaceutical formulation as claimed in claims 50 to 54, wherein the neoplasia is a precancerous lesion including syndromes represented by

abnormal neoplastic and/or dysplastic, changes of tissue comprising precancerous growths in colonic, breast, renal, central nervous, gastric, or lung tissues, or conditions such as dysplastic nevus syndrome, a precursor to malignant melanoma of the skin, dysplastic nevus syndromes, polyposis syndromes, colonic polyps, precancerous lesions of the cervix (i.e., cervical dysplasia), prostatic dysplasia, bronchial dysplasia, breast, bladder and/or skin and related conditions (e.g., actinic keratosis), whether the lesions are clinically identifiable or not.

56. The use of a pharmaceutical formulation as claimed in claims 50 to 55, wherein the neoplasia is prostate cancer, colon cancer, small cell lung cancer, large cell lung cancer, lung adenocarcinoma, epidermoid lung cancer, melanoma (including amelanotic subtypes), renal cell carcinoma, gastric carcinoma, cancers of the central nervous system including brain tumours, neuroblastomas, gastric carcinoma, breast cancer, ovarian cancer, testicular cancer, lymphoma and leukaemia, oesophageal cancer, stomach cancer, liver cancers, prostate cancer, cervical cancer, adrenal cancer, oral or mucosal cancer, bladder cancer, pancreatic cancer, lymphoma, Hodgkins disease, sarcomas. Hematopoeitic cell cancers such as B cell leukaemia/lymphomas, myelomas, T-cell leukemias/lymphomas, small cell leukemias/lymphomas, null cell, sezary, monocytic, myelomonocytic and Hairy cell leukemias.

57. The use of a pharmaceutical formulation as claimed in claims 50 to 56, wherein the neoplasia is in the form of a tumour comprising an epidermoid and myeloid tumour, acute or chronic, nonsmall cell , squamous or solid.

58. The use of a pharmaceutical formulation as claimed in claims 50 to 57, wherein the composition is micronized.

59. The use of a pharmaceutical formulation as claimed In claims 50 to 58, wherein the pharmaceutical formulation has an enteric coating.

60. The use of a pharmaceutical formulation as claimed in claim 59, wherein the enteric coating Is made of a polymer or copolymer.

61. The use of a pharmaceutical formulation as claimed in claim 60, wherein the polymer or copolymer is selected from the group consisting of poly(lactic-glycolic acid) polyester, cellulose acetate phthalate, hydroxypropyl-methyl cellulose phthalate poly(butyl methacrylate), (2-dimethyl aminoethyl) methacrylate, and methyl methacrylate.

62. The use of a pharmaceutical formulation as claimed in claims 50 to 61, wherein, the pharmaceutical formulation is administered enterally, parenterally, topically, orally, sub-lingually, rectally, nasally or vaginally.

63. The use of a pharmaceutical formulation as claimed in claims 50 to 62, wherein the composition is formulated into liposomes or carbohydrate vehicles.

64. The use of a pharmaceutical formulation as claimed in claim 63, wherein the liposomes or carbohydrate vehicles are specifically targeted to tumours by covalently attaching a monoclonal antibody directed to a tumour-associated antigen.

65. The use of a pharmaceutical formulation as claimed in claims 50 to 64, wherein the pharmaceutical formulation is administered intermittently.

66. The use of a pharmaceutical formulation as claimed in claims 50 to 65, wherein the pharmaceutical formulation is a unit dose that comprises 5-500 mg of active ingredient consisting of at least one compound of the present invention.

67. The use of a pharmaceutical formulation as claimed in claims 50 to 66, wherein the pharmaceutical formulation is administered to a mammal.

68. The use of a pharmaceutical formulation as claimed in claim 67, wherein said mammal is a neonate and said administering is effected prior to delivery of said neonate and/or during delivery of said neonate.

69. The use of a pharmaceutical formulation as claimed in claims 50 to 68, wherein the composition acts as a prodrug.